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**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

**THERAPEUTICSMD, INC.,**

**Plaintiff,**

**v.**

**AMNEAL PHARMACEUTICALS, INC.,  
AMNEAL PHARMACEUTICALS, LLC,  
and AMNEAL PHARMACEUTICALS OF  
NEW YORK LLC,**

**Defendants.**

**Civil Action No. 20-5256 (FLW)(TJB)**

**AMENDED COMPLAINT FOR  
PATENT INFRINGEMENT**

**(Filed Electronically)**

Plaintiff TherapeuticsMD, Inc. (“TherapeuticsMD”), by its undersigned attorneys, for its Complaint against defendants Amneal Pharmaceuticals, Inc. (“Amneal Inc.”), Amneal Pharmaceuticals, LLC (“Amneal LLC”), and Amneal Pharmaceuticals of New York LLC (“Amneal NY”) (together, “Amneal” or “Defendants”), alleges as follows:

### **Nature of the Action**

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. § 100, *et seq.*, arising from the filing of Abbreviated New Drug Application (“ANDA”) No. 214293 (“Amneal’s ANDA”) with the United States Food and Drug Administration (“FDA”) seeking approval to commercially market a generic version of TherapeuticsMD’s BIJUVA<sup>®</sup> drug product (“Amneal’s Proposed Product”) before the expiration of United States Patent Nos. 8,633,178 (the “178 patent”); 8,846,648 (the “648 patent”); 8,846,649 (the “649 patent”); 8,987,237 (the “237 patent”); 8,993,548 (the “548 patent”); 8,993,549 (the “549 patent”); 9,006,222 (the “222 patent”); 9,114,145 (the “145 patent”); 9,114,146 (the “146 patent”); 9,301,920 (the “920 patent”); 10,052,386 (the “386 patent”); 10,206,932 (the “932 patent”); and 10,639,375 (the “375 patent”) (collectively, “the patent(s)-in-suit”), all owned by TherapeuticsMD.

### **The Parties**

2. Plaintiff TherapeuticsMD is a women’s healthcare company committed to creating and commercializing innovative products to support women from pregnancy prevention through menopause. TherapeuticsMD focuses on, and invests heavily in, the development and commercialization of health solutions that enable new standards of care for women.

TherapeuticsMD is a corporation organized and existing under the laws of the State of Nevada, having a principal place of business at 951 Yamato Rd., Suite 220, Boca Raton, Florida 33431.

3. On information and belief, Defendant Amneal Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 400 Crossing Boulevard, Bridgewater, New Jersey 08807.

4. On information and belief, Defendant Amneal LLC is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of

business at 400 Crossing Boulevard, Bridgewater, New Jersey 08807. On information and belief, Amneal LLC is a wholly owned subsidiary of Amneal Inc.

5. On information and belief, Defendant Amneal NY is a limited liability company organized and existing under the laws of the State of Delaware, having a place of business at 400 Crossing Blvd., Third Floor, Bridgewater, New Jersey 08807. On information and belief, Amneal NY is a wholly owned subsidiary of Amneal LLC.

### **The Patents-in-Suit**

6. On January 21, 2014, the United States Patent and Trademark Office (“USPTO”) duly and lawfully issued the ’178 patent, entitled, “Natural Combination Hormone Replacement Formulations and Therapies,” to TherapeuticsMD as assignee of the inventors. A copy of the ’178 patent is attached hereto as Exhibit A.

7. On September 30, 2014, the USPTO duly and lawfully issued the ’648 patent, entitled, “Natural Combination Hormone Replacement Formulations and Therapies,” to TherapeuticsMD as assignee of the inventors. A copy of the ’648 patent is attached hereto as Exhibit B.

8. On September 30, 2014, the USPTO duly and lawfully issued the ’649 patent, entitled, “Natural Combination Hormone Replacement Formulations and Therapies,” to TherapeuticsMD as assignee of the inventors. A copy of the ’649 patent is attached hereto as Exhibit C.

9. On March 24, 2015, the USPTO duly and lawfully issued the ’237 patent, entitled, “Natural Combination Hormone Replacement Formulations and Therapies,” to TherapeuticsMD as assignee of the inventors. A copy of the ’237 patent is attached hereto as Exhibit D.

10. On March 31, 2015, the USPTO duly and lawfully issued the '548 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '548 patent is attached hereto as Exhibit E.

11. On March 31, 2015, the USPTO duly and lawfully issued the '549 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '549 patent is attached hereto as Exhibit F.

12. On April 14, 2015, the USPTO duly and lawfully issued the '222 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '222 patent is attached hereto as Exhibit G.

13. On August 25, 2015, the USPTO duly and lawfully issued the '145 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '145 patent is attached hereto as Exhibit H.

14. On August 25, 2015, the USPTO duly and lawfully issued the '146 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '146 patent is attached hereto as Exhibit I.

15. On April 5, 2016, the USPTO duly and lawfully issued the '920 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '920 patent is attached hereto as Exhibit J.

16. On August 21, 2018, the USPTO duly and lawfully issued the '386 patent, entitled, "Progesterone Formulations," to TherapeuticsMD as assignee of the inventors. A copy of the '386 patent is attached hereto as Exhibit K.

17. On February 19, 2019, the USPTO duly and lawfully issued the '932 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies," to TherapeuticsMD as assignee of the inventors. A copy of the '932 patent is attached hereto as Exhibit L.

18. On May 5, 2020, the USPTO duly and lawfully issued the '375 patent, entitled, "Progesterone Formulations," to TherapeuticsMD as assignee of the inventors. A copy of the '375 patent is attached hereto as Exhibit M.

**The BIJUVA<sup>®</sup> Drug Product**

19. TherapeuticsMD holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for estradiol and progesterone capsules (NDA No. 210132), which it sells under the trade name BIJUVA<sup>®</sup>. BIJUVA<sup>®</sup> is an FDA-approved medication indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

20. The claims of the patents-in-suit cover, *inter alia*, pharmaceutical compositions and formulations comprising estradiol and progesterone, pharmaceutical compositions comprising progesterone, and methods of use of pharmaceutical compositions comprising estradiol and progesterone.

21. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the patents-in-suit are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to BIJUVA<sup>®</sup>.

**Jurisdiction and Venue**

22. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

23. TherapeuticsMD received a letter from Amneal no earlier than March 17, 2020, notifying TherapeuticsMD that Amneal submitted ANDA No. 214293 (“Amneal’s Notice Letter”). Each page of Amneal’s Notice Letter bears the address 400 Crossing Boulevard, 3rd Floor, Bridgewater, NJ 08807.

24. Attached to the Amneal Notice Letter was a document entitled “Amneal Pharmaceuticals, LLC Detailed Factual and Legal Basis of Non-Infringement and/or Invalidity” (“Amneal’s Detailed Statement”).

25. On information and belief, one or more acts related to Amneal’s preparation of Amneal’s ANDA and the preparation of Amneal’s written certifications to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (“Amneal’s Paragraph IV Certification(s)”), set forth in Amneal’s ANDA were conducted in this District and/or will be conducted in the District.

26. On information and belief, upon FDA approval of Amneal’s ANDA, Amneal intends to commercially manufacture, import, market, offer for sale, and/or sell Amneal’s Proposed Product throughout the United States including in this Judicial District.

27. On information and belief, Amneal is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District. This Judicial District is a likely destination for the generic drug products described in ANDA No. 214293. On information and belief, Amneal also prepares and/or aids in the preparation and submission of ANDAs to the FDA.

28. The Court has personal jurisdiction over Amneal LLC by virtue of, *inter alia*, its continuous and systematic contacts with the State of New Jersey. On information and belief, Amneal LLC's principal place of business is in Bridgewater, New Jersey. On information and belief, Amneal LLC is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business I.D. No. 0600211542. On information and belief, Amneal LLC is registered with the State of New Jersey's Department of Health as a drug manufacturer and wholesaler, under Registration No. 5002991. On information and belief, Amneal LLC purposefully has conducted and continues to conduct business in this Judicial District.

29. This Court has personal jurisdiction over Amneal NY because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in New Jersey, including directly or indirectly through its affiliate, agent, and/or alter ego, Amneal LLC, a company that has its principal place of business in the State of New Jersey and holds licenses with the State of New Jersey as a pharmacy wholesaler; and (2) maintains extensive and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Amneal LLC. On information and belief, Amneal NY has a place of business at 400 Crossing Blvd., Third Floor, Bridgewater, New Jersey 08807. On information and belief, Amneal NY is registered with the State of New Jersey's Department of Health as a drug manufacturer and wholesaler, under Registration No. 5003663. On information and belief, Amneal NY purposefully has conducted and continues to conduct business in this Judicial District.

30. This Court has personal jurisdiction over Amneal Inc. because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in New Jersey, including

directly or indirectly through its subsidiaries, agents, and/or alter egos, Amneal LLC, a company that has its principal place of business in the State of New Jersey and holds licenses with the State of New Jersey as a pharmacy wholesaler, and Amneal NY, a company that has a place of business in the State of New Jersey and is registered with the State of New Jersey as a drug manufacturer and wholesaler; and (2) maintains extensive and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Amneal LLC and/or Amneal NY.

31. On information and belief, Amneal Inc.'s executive offices are located in Bridgewater, New Jersey. On information and belief, Amneal Inc. owns or leases numerous properties throughout New Jersey for the purposes of manufacturing, research and development, warehousing, and packaging. (*See* Amneal Pharmaceuticals, Inc. Securities and Exchange Commission Form 10-K (for the fiscal year ended December 31, 2019) ("Amneal Inc. Form 10-K") at 34.)

32. On information and belief, Amneal Inc. regularly and continuously transacts business within New Jersey, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey. On information and belief, Amneal Inc. derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey. Amneal Inc.'s 10-K filing states, "[t]he Company's Generics segment includes over 200 product families covering an extensive range of dosage forms and delivery systems . . . [and] 113 products either approved but not yet launched or pending FDA approval." (Amneal Inc. Form 10-K at 5.) On information and belief, Amneal Inc. derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.



33. This Court has personal jurisdiction over Amneal because, *inter alia*, it has committed an act of patent infringement under 35 U.S.C. § 271(e)(2), and has sent notice of that infringement to TherapeuticsMD. On information and belief, Amneal intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will continue to lead to foreseeable harm and injury to TherapeuticsMD in New Jersey and in this Judicial District. For example, on information and belief, Amneal will work towards the regulatory approval, manufacturing, use, importation, marketing, sale, offer for sale, and distribution of generic pharmaceutical products, including Amneal's ANDA Product, throughout the United States, including in New Jersey and in this Judicial District, before the expiration of the patents-in-suit.

34. In Amneal's Notice Letter, Amneal stated that the name and address of its agent in the United States authorized to accept written notice requesting access under its Office of Confidential Access is Lars Taavola, Esq., Amneal Pharmaceuticals, LLC, 400 Crossing Boulevard, 3<sup>rd</sup> Floor, Bridgewater, NJ 08807. By naming Mr. Taavola in Bridgewater, NJ as its agent in connection with this action, Amneal has consented to jurisdiction in New Jersey.

35. Amneal LLC has previously been sued in this Judicial District, has availed itself of New Jersey courts through its assertion of counterclaims in suits brought in New Jersey, and has not challenged personal jurisdiction. *See, e.g., Cubist Pharmaceuticals LLC v. Amneal Pharmaceuticals, LLC, et al.* No. 19-15439 (D.N.J.); *Senju Pharmaceutical Co., et al. v. Amneal Pharmaceuticals LLC et al.*, No. 18-05571 (D.N.J.); *BTG International Limited, et al. v. Actavis Laboratories FL, Inc., et al.*, No. 15- 05909 (D.N.J.); *Shire Pharmaceutical Development Inc., et al. v. Amneal Pharmaceuticals LLC, et al.*, No. 15-02865 (D.N.J.); *Novo Nordisk Inc., et al. v.*

*Amneal Pharmaceuticals, LLC, et al.*, No. 13-04915 (D.N.J.); *Luitpold Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, et al.*; No. 12-05064 (D.N.J.).

36. Amneal LLC has further availed itself of the jurisdiction of this Court by initiating litigation in this Judicial District. *See, e.g., Amneal Pharmaceuticals LLC v. Reckitt Benckiser Pharmaceuticals, Inc., et al.*, No. 15-08864 (D.N.J.).

37. Amneal NY has previously been sued in this Judicial District, has availed itself of New Jersey courts through its assertion of counterclaims in suits brought in New Jersey, and has not challenged personal jurisdiction. *See, e.g., BTG International Limited et al. v. Actavis Laboratories FL, Inc.. et al.*, No. 15- 05909 (D.N.J.); *Shire Pharmaceutical Development Inc., et al. v. Amneal Pharmaceuticals LLC, et al.*, No. 15-02865 (D.N.J.); *Novo Nordisk Inc., et al. v. Amneal Pharmaceuticals, LLC, et al.*, No. 13-04915 (D.N.J.); *Luitpold Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, et al.*; No. 12-05064 (D.N.J.).

38. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and/or 1400(b).

#### **Acts Giving Rise To This Suit**

39. Pursuant to Section 505 of the FFDCA, Amneal's ANDA seeks FDA approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of 1 mg/100 mg (estradiol/progesterone) capsules before the patents-in-suit expire.

40. On information and belief, following FDA approval of Amneal's ANDA, Amneal will make, use, offer to sell, or sell Amneal's Proposed Product throughout the United States, or import such generic products into the United States.

41. On information and belief, the proposed label or proposed package insert for Amneal's Proposed Product states that it is indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

42. On information and belief, in connection with the filing of its ANDA as described above, Amneal provided Amneal's Paragraph IV Certification(s) alleging, *inter alia*, that the claims of the patent(s)-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Amneal's ANDA.

43. No earlier than March 17, 2020, TherapeuticsMD received Amneal's written notice of its Paragraph IV Certification(s). Amneal's Notice Letter alleged, *inter alia*, that the claims of the patent(s)-in-suit are invalid and/or will not be infringed by the activities described in Amneal's ANDA. Amneal's Notice Letter also informed TherapeuticsMD that Amneal seeks approval to market Amneal's Proposed Product before the patent(s)-in-suit expire. Amneal's Notice Letter also requested that any correspondence regarding Amneal's Offer of Confidential Access to its ANDA pursuant to 21 U.S.C. § 355(j)(5)(C) be sent to Amneal at 400 Crossing Boulevard in Bridgewater, NJ 08807.

**Count I: Infringement of the '178 Patent**

44. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

45. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '178 patent.

46. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

47. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before

the expiration of the '178 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

48. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '178 patent.

49. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '178 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

50. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '178 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '178 patent and knowledge that its acts are encouraging infringement.

51. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '178 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '178 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

52. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '178 patent is not enjoined.

53. TherapeuticsMD does not have an adequate remedy at law.

54. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count II: Infringement of the '648 Patent**

55. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

56. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '648 patent.

57. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

58. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '648 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

59. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '648 patent.

60. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '648 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

61. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '648 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will

intentionally encourage acts of direct infringement with knowledge of the '648 patent and knowledge that its acts are encouraging infringement.

62. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '648 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '648 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

63. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '648 patent is not enjoined.

64. TherapeuticsMD does not have an adequate remedy at law.

65. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count III: Infringement of the '649 Patent**

66. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

67. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '649 patent.

68. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

69. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '649 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

70. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '649 patent.

71. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '649 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

72. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '649 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '649 patent and knowledge that its acts are encouraging infringement.

73. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '649 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '649 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

74. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '649 patent is not enjoined.

75. TherapeuticsMD does not have an adequate remedy at law.

76. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count IV: Infringement of the '237 Patent**

77. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

78. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '237 patent.

79. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

80. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '237 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

81. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '237 patent.

82. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '237 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.



83. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '237 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '237 patent and knowledge that its acts are encouraging infringement.

84. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '237 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '237 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

85. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '237 patent is not enjoined.

86. TherapeuticsMD does not have an adequate remedy at law.

87. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count V: Infringement of the '548 Patent**

88. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

89. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial

manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '548 patent.

90. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

91. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '548 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

92. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '548 patent.

93. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '548 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

94. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '548 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '548 patent and knowledge that its acts are encouraging infringement.

95. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '548 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that

Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '548 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

96. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '548 patent is not enjoined.

97. TherapeuticsMD does not have an adequate remedy at law.

98. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count VI: Infringement of the '549 Patent**

99. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

100. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '549 patent.

101. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

102. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '549 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

103. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '549 patent.

104. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '549 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

105. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '549 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '549 patent and knowledge that its acts are encouraging infringement.

106. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '549 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '549 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

107. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '549 patent is not enjoined.

108. TherapeuticsMD does not have an adequate remedy at law.

109. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count VII: Infringement of the '222 Patent**

110. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

111. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '222 patent.

112. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

113. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '222 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

114. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '222 patent.

115. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '222 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

116. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '222 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '222 patent and knowledge that its acts are encouraging infringement.

117. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '222 patent under 35 U.S.C. § 271(c) by

making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '222 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

118. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '222 patent is not enjoined.

119. TherapeuticsMD does not have an adequate remedy at law.

120. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count VIII: Infringement of the '145 Patent**

121. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

122. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '145 patent.

123. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

124. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '145 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

125. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '145 patent.

126. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '145 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

127. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '145 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '145 patent and knowledge that its acts are encouraging infringement.

128. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '145 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '145 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

129. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '145 patent is not enjoined.

130. TherapeuticsMD does not have an adequate remedy at law.

131. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count IX: Infringement of the '146 Patent**

132. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

133. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '146 patent.

134. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

135. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '146 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

136. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '146 patent.

137. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '146 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

138. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '146 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '146 patent and knowledge that its acts are encouraging infringement.



139. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '146 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '146 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

140. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '146 patent is not enjoined.

141. TherapeuticsMD does not have an adequate remedy at law.

142. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count X: Infringement of the '920 Patent**

143. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

144. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '920 patent.

145. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

146. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before

the expiration of the '920 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

147. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '920 patent.

148. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '920 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

149. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '920 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '920 patent and knowledge that its acts are encouraging infringement.

150. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '920 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '920 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

151. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '920 patent is not enjoined.

152. TherapeuticsMD does not have an adequate remedy at law.

153. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count XI: Infringement of the '386 Patent**

154. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

155. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '386 patent.

156. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

157. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '386 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

158. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '386 patent.

159. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '386 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

160. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '386 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will

intentionally encourage acts of direct infringement with knowledge of the '386 patent and knowledge that its acts are encouraging infringement.

161. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '386 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '386 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

162. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '386 patent is not enjoined.

163. TherapeuticsMD does not have an adequate remedy at law.

164. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count XII: Infringement of the '932 Patent**

165. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

166. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '932 patent.

167. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

168. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '932 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

169. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '932 patent.

170. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '932 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

171. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '932 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '932 patent and knowledge that its acts are encouraging infringement.

172. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '932 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '932 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

173. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '932 patent is not enjoined.

174. TherapeuticsMD does not have an adequate remedy at law.

175. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

**Count XIII: Infringement of the '375 Patent**

176. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

177. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

178. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '375 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

179. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '375 patent.

180. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '375 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

181. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '375 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will

intentionally encourage acts of direct infringement with knowledge of the '375 patent and knowledge that its acts are encouraging infringement.

182. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '375 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '375 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

183. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '375 patent is not enjoined.

184. TherapeuticsMD does not have an adequate remedy at law.

185. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

#### **PRAYER FOR RELIEF**

WHEREFORE, Plaintiff TherapeuticsMD respectfully requests the following relief:

(A) A Judgment that Amneal has infringed the patents-in-suit by submitting ANDA No. 214293;

(B) A Judgment that Amneal has infringed, and that Amneal's making, using, offering to sell, selling, or importing Amneal's Proposed Product will infringe one or more claims of the patents-in-suit;

(C) An Order that the effective date of FDA approval of ANDA No. 214293 be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which TherapeuticsMD is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Amneal and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing Amneal's Proposed Product until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which TherapeuticsMD is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Amneal, its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from practicing any of the claimed inventions of the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which TherapeuticsMD is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Amneal's Proposed Product will directly infringe, induce, and/or contribute to infringement of the patents-in-suit;

(G) To the extent that Amneal has committed any acts with respect to the claimed inventions of the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding TherapeuticsMD damages for such acts;

(H) If Amneal engages in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Amneal's Proposed Product before the expiration of the patents-in-suit, a Judgment awarding damages to TherapeuticsMD resulting from such infringement, together with interest;

(I) A Judgment declaring that the patents-in-suit remain valid and enforceable;



(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding TherapeuticsMD its attorneys' fees incurred in this action;

(K) A Judgment awarding TherapeuticsMD its costs and expenses incurred in this action; and

(L) Such further and other relief as this Court may deem just and proper.

Dated: May 20, 2020

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**CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1**

I hereby certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: May 20, 2020

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# **EXHIBIT A**



US008633178B2

(12) **United States Patent**  
**Bernick et al.**

(10) **Patent No.:** **US 8,633,178 B2**  
(45) **Date of Patent:** **Jan. 21, 2014**

(54) **NATURAL COMBINATION HORMONE  
REPLACEMENT FORMULATIONS AND  
THERAPIES**

(71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL  
(US)

(72) Inventors: **Brian A. Bernick**, Boca Raton, FL (US);  
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FL (US)

(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL  
(US)

(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/684,002**

(22) Filed: **Nov. 21, 2012**

(65) **Prior Publication Data**

US 2013/0129818 A1 May 23, 2013

**Related U.S. Application Data**

(60) Provisional application No. 61/563,408, filed on Nov.  
23, 2011, provisional application No. 61/661,302,  
filed on Jun. 18, 2012, provisional application No.  
61/662,265, filed on Jun. 20, 2012.

(51) **Int. Cl.**  
**A01N 45/00** (2006.01)  
**A61K 9/48** (2006.01)

(52) **U.S. Cl.**  
USPC ..... **514/169; 424/452**

(58) **Field of Classification Search**  
None  
See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

1,967,351 A 7/1934 Dolay  
2,232,438 A 2/1941 Butenandt  
2,379,832 A 7/1945 Serini et al.  
2,649,399 A 8/1953 Beall et al.  
3,198,707 A 8/1965 Nomine et al.  
3,478,070 A 11/1969 Stein et al.  
3,526,648 A 9/1970 Bertin et al.  
3,710,795 A 1/1973 Higuchi et al.  
3,729,560 A 4/1973 Hagerman  
3,729,566 A 4/1973 Ericsson et al.  
3,755,573 A 8/1973 Berman  
3,755,575 A 8/1973 Lerner  
3,903,880 A 9/1975 Higuchi et al.  
3,916,898 A 11/1975 Robinson  
3,916,899 A 11/1975 Theeuwes et al.  
3,921,636 A 11/1975 Zaffaroni  
3,923,997 A 12/1975 Meuly  
3,948,254 A 4/1976 Zaffaroni  
3,971,367 A 7/1976 Zaffaroni  
3,977,404 A 8/1976 Theeuwes

3,993,072 A 11/1976 Zaffaroni  
4,008,719 A 2/1977 Theeuwes et al.  
4,012,496 A 3/1977 Schopflin et al.  
4,014,334 A 3/1977 Theeuwes et al.  
4,014,987 A 3/1977 Heller et al.  
4,016,251 A 4/1977 Higuchi et al.  
4,071,623 A 1/1978 van der Vies  
4,093,709 A 6/1978 Choi et al.  
4,154,820 A 5/1979 Simoons  
4,155,991 A 5/1979 Schopflin et al.  
4,196,188 A 4/1980 Besins  
4,215,691 A 8/1980 Wong  
4,237,885 A 12/1980 Wong et al.  
4,310,510 A 1/1982 Sherman et al.  
4,327,725 A 5/1982 Cortese et al.  
4,372,951 A 2/1983 Vorys  
4,393,871 A 7/1983 Vorhauer et al.  
4,402,695 A 9/1983 Wong  
4,423,151 A 12/1983 Baranczuk  
4,449,980 A 5/1984 Millar et al.  
4,610,687 A 9/1986 Fogwell  
4,629,449 A 12/1986 Wong  
4,732,763 A 3/1988 Beck et al.  
4,738,957 A 4/1988 Laurent et al.  
4,756,907 A 7/1988 Beck et al.  
4,762,717 A 8/1988 Crowley, Jr.  
4,788,062 A 11/1988 Gale et al.  
4,816,257 A 3/1989 Buster et al.  
4,822,616 A 4/1989 Zimmermann et al.  
4,865,848 A 9/1989 Cheng et al.

(Continued)

**FOREIGN PATENT DOCUMENTS**

CN 102258455 11/2011  
EP 0275716 A1 7/1988  
EP 0622075 A1 11/1994  
EP 0785211 A1 1/1996  
EP 0785212 A1 1/1996  
EP 0811381 A1 6/1997  
EP 2191833 A1 6/2010  
GB 720561 12/1954  
GB 848881 A1 9/1960  
GB 874368 8/1961

(Continued)

**OTHER PUBLICATIONS**

Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal  
Drug Delivery," Drug Development and Industrial Pharmacy,  
35(5):525-547. 2009. Abstract Only.

(Continued)

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(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are pro-  
vided herein. Among others, the following formulations are  
provided herein: solubilized estradiol without progesterone;  
micronized progesterone without estradiol; micronized  
progesterone with partially solubilized progesterone; solubi-  
lized estradiol with micronized progesterone; solubilized  
estradiol with micronized progesterone in combination with  
partially solubilized progesterone; and solubilized estradiol  
with solubilized progesterone.

**6 Claims, 4 Drawing Sheets**

## US 8,633,178 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

4,900,734	A *	2/1990	Maxson et al. .... 514/171	6,039,968	A	3/2000	Nabahi
4,906,475	A	3/1990	Kim	6,056,972	A	5/2000	Hermismeyer
4,942,158	A	7/1990	Sarpotdar et al.	6,060,077	A	5/2000	Meignant
4,961,931	A	10/1990	Wong	6,074,625	A	6/2000	Hawthorne et al.
5,030,629	A	7/1991	Rajadhyaksha	6,077,531	A	6/2000	Salin-Drouin
5,064,654	A	11/1991	Berner et al.	6,080,118	A	6/2000	Blythe
5,108,995	A	4/1992	Casper	6,083,178	A	7/2000	Caillouette
5,128,138	A	7/1992	Blank	6,086,916	A	7/2000	Agnus et al.
5,130,137	A	7/1992	Crowley, Jr.	6,096,338	A	8/2000	Lacy et al.
5,140,021	A	8/1992	Maxson et al.	6,117,446	A	9/2000	Place
5,211,952	A	5/1993	Spicer et al.	6,117,450	A	9/2000	Dittgen et al.
5,252,334	A	10/1993	Chiang et al.	6,133,251	A	10/2000	Dittgen et al.
5,280,023	A	1/1994	Ehrlich et al.	6,133,320	A	10/2000	Yallampalli et al.
5,288,496	A	2/1994	Lewis	6,139,873	A	10/2000	Hughes, Jr. et al.
5,340,584	A	8/1994	Spicer et al.	6,153,216	A	11/2000	Cordes et al.
5,340,585	A	8/1994	Pike et al.	6,165,491	A	12/2000	Grasset et al.
5,340,586	A	8/1994	Pike et al.	6,165,975	A	12/2000	Adams et al.
5,362,497	A	11/1994	Yamada et al.	6,187,339	B1	2/2001	de Haan et al.
5,382,573	A	1/1995	Casper	6,190,331	B1	2/2001	Caillouette
5,393,528	A	2/1995	Staab	6,201,072	B1	3/2001	Rathi et al.
5,393,529	A	2/1995	Hoffmann et al.	6,227,202	B1	5/2001	Matapurkar
5,419,910	A	5/1995	Lewis	6,262,115	B1	7/2001	Guittard et al.
5,468,736	A	11/1995	Hodgen	6,277,418	B1	8/2001	Markaverich et al.
5,474,783	A	12/1995	Miranda et al.	6,283,927	B1	9/2001	Caillouette
5,480,776	A	1/1996	Dullien	6,287,588	B1	9/2001	Shih et al.
5,514,673	A	5/1996	Heckenmuller et al.	6,287,693	B1	9/2001	Savoir et al.
5,516,528	A	5/1996	Hughes et al.	6,294,188	B1	9/2001	Ragavan et al.
5,527,534	A	6/1996	Myhling	6,294,550	B1	9/2001	Place et al.
5,529,782	A	6/1996	Staab	6,299,900	B1	10/2001	Reed et al.
5,543,150	A	8/1996	Bologna et al.	6,306,841	B1	10/2001	Place et al.
5,547,948	A	8/1996	Barcomb	6,306,914	B1	10/2001	de Ziegler et al.
5,565,199	A	10/1996	Page et al.	6,309,669	B1	10/2001	Setterstrom et al.
5,567,831	A	10/1996	Li	6,309,848	B1	10/2001	Howett et al.
5,569,652	A	10/1996	Beier et al.	6,342,491	B1	1/2002	Dey et al.
5,582,592	A	12/1996	Kendrick	6,372,209	B1	4/2002	Chrisope
5,585,370	A	12/1996	Casper	6,372,246	B1	4/2002	Wei et al.
5,595,759	A	1/1997	Wright et al.	6,387,390	B1	5/2002	Deaver et al.
5,595,970	A	1/1997	Garfield et al.	6,402,705	B1	6/2002	Caillouette
5,620,705	A	4/1997	Dong et al.	6,416,778	B1	7/2002	Ragavan et al.
5,629,021	A	5/1997	Wright	6,423,039	B1	7/2002	Rathbone et al.
5,633,011	A	5/1997	Dong et al.	6,423,683	B1	7/2002	Heaton et al.
5,633,242	A	5/1997	Oettel et al.	6,436,633	B1	8/2002	Kreider et al.
5,639,743	A	6/1997	Kaswan et al.	6,440,454	B1	8/2002	Santoro et al.
5,656,286	A	8/1997	Miranda et al.	6,444,224	B1	9/2002	Rathbone et al.
5,676,968	A	10/1997	Lipp et al.	6,451,339	B2	9/2002	Patel et al.
5,677,292	A	10/1997	Li et al.	6,451,779	B1	9/2002	Hesch
5,694,947	A	12/1997	Lehtinen et al.	6,455,246	B1	9/2002	Howett et al.
5,709,844	A	1/1998	Arbeit et al.	6,455,517	B1	9/2002	Tanabe et al.
5,735,801	A	4/1998	Caillouette	6,468,526	B2	10/2002	Chrisope
5,739,176	A	4/1998	Dunn et al.	6,469,016	B1	10/2002	Place et al.
5,744,463	A	4/1998	Bair	6,472,434	B1	10/2002	Place et al.
5,747,058	A	5/1998	Tipton et al.	6,479,232	B1	11/2002	Howett et al.
5,770,219	A	6/1998	Chiang et al.	6,500,814	B1	12/2002	Hesch
5,776,495	A	7/1998	Duclos et al.	6,503,896	B1	1/2003	Tanabe et al.
5,788,980	A	8/1998	Nabahi	6,526,980	B1	3/2003	Tracy et al.
5,789,442	A	8/1998	Garfield et al.	6,528,094	B1	3/2003	Savoir et al.
5,811,416	A	9/1998	Chwalisz et al.	6,537,580	B1	3/2003	Savoir et al.
5,814,329	A	9/1998	Shah	6,544,196	B2	4/2003	Caillouette
5,827,200	A	10/1998	Caillouette	6,544,553	B1	4/2003	Hsia et al.
5,866,603	A	2/1999	Li et al.	6,548,491	B2	4/2003	Tanabe et al.
5,891,868	A	4/1999	Cummings et al.	6,551,611	B2	4/2003	Elliesen et al.
5,898,038	A	4/1999	Yallampalli et al.	6,569,463	B2	5/2003	Patel et al.
5,916,176	A	6/1999	Caillouette	6,583,129	B1	6/2003	Mazer et al.
RE36,247	E	7/1999	Plunkett et al.	6,586,006	B2	7/2003	Roser et al.
5,922,349	A	7/1999	Elliesen et al.	6,589,549	B2	7/2003	Shih et al.
5,928,666	A	7/1999	Farinas et al.	6,593,317	B1	7/2003	de Ziegler et al.
5,958,446	A	9/1999	Miranda et al.	6,610,652	B2	8/2003	Adams et al.
5,962,445	A	10/1999	Stewart	6,610,670	B2	8/2003	Backensfeld et al.
5,972,372	A	10/1999	Saleh et al.	6,638,536	B2	10/2003	Savoir et al.
5,985,861	A	11/1999	Levine et al.	6,645,528	B1	11/2003	Straub et al.
5,993,856	A	11/1999	Ragavan et al.	6,653,298	B2	11/2003	Potter et al.
6,001,846	A	12/1999	Edwards et al.	6,656,929	B1	12/2003	Agnus et al.
6,022,562	A	2/2000	Autant et al.	6,660,726	B2	12/2003	Hill et al.
6,024,976	A	2/2000	Miranda et al.	6,663,608	B2	12/2003	Rathbone et al.
6,028,057	A	2/2000	Burns	6,663,895	B2	12/2003	Savoir et al.
				6,692,763	B1	2/2004	Cummings et al.
				6,737,081	B2	5/2004	Savoir et al.
				6,740,333	B2	5/2004	Beckett et al.
				6,743,815	B2	6/2004	Huebner et al.

## US 8,633,178 B2

Page 3

(56)

## References Cited

## U.S. PATENT DOCUMENTS

6,747,018 B2	6/2004	Tanabe et al.	7,727,720 B2	6/2010	Dhallan
6,756,208 B2	6/2004	Griffin et al.	7,732,408 B2	6/2010	Josephson et al.
6,776,164 B2	8/2004	Bunt et al.	7,749,989 B2	7/2010	Hill et al.
6,805,877 B2	10/2004	Massara et al.	7,767,656 B2	8/2010	Shoichet et al.
6,809,085 B1	10/2004	Elson et al.	7,815,949 B2	10/2010	Cohen
6,818,226 B2	11/2004	Reed et al.	7,829,115 B2	11/2010	Besins et al.
6,841,716 B1	1/2005	Tsutsumi	RE42,012 E	12/2010	Deaver et al.
6,844,334 B2	1/2005	Hill et al.	7,858,607 B2	12/2010	Mamchur
6,855,703 B1	2/2005	Hill et al.	RE42,072 E	1/2011	Deaver et al.
6,860,859 B2	3/2005	Mehrotra et al.	7,862,552 B2	1/2011	McIntyre et al.
6,866,865 B2	3/2005	Hsia et al.	7,867,990 B2	1/2011	Schultz et al.
6,869,969 B2	3/2005	Huebner et al.	7,879,830 B2	2/2011	Wiley
6,878,518 B2	4/2005	Whitehead	7,884,093 B2	2/2011	Creasy et al.
6,901,278 B1	5/2005	Notelovitz	7,939,104 B2	5/2011	Barbera et al.
6,905,705 B2	6/2005	Palm et al.	7,943,602 B2	5/2011	Bunschoten et al.
6,911,438 B2	6/2005	Wright	7,943,604 B2	5/2011	Coelingh Bennink et al.
6,923,988 B2	8/2005	Patel et al.	7,989,436 B2	8/2011	Hill et al.
6,924,274 B2	8/2005	Lardy et al.	7,989,487 B2	8/2011	Welsh et al.
6,932,983 B1	8/2005	Straub et al.	8,022,053 B2	9/2011	Mueller et al.
6,939,558 B2	9/2005	Massara et al.	8,048,869 B2	11/2011	Bunschoten et al.
6,943,021 B2	9/2005	Klausner et al.	8,071,729 B2	12/2011	Giles-Komar et al.
6,958,327 B1	10/2005	Hillisch et al.	8,076,319 B2	12/2011	Leonard
6,962,691 B1	11/2005	Lulla et al.	8,088,605 B2	1/2012	Beaudet et al.
6,962,908 B2	11/2005	Aloba et al.	8,101,209 B2	1/2012	Legrand et al.
6,967,194 B1	11/2005	Matsuo et al.	8,114,434 B2	2/2012	Sasaki et al.
6,977,250 B2	12/2005	Rodriguez	8,158,614 B2	4/2012	Lambert et al.
6,978,945 B2	12/2005	Wong et al.	8,202,736 B2	6/2012	Mousa et al.
7,005,429 B2	2/2006	Dey et al.	8,217,024 B2	7/2012	Ahmed et al.
7,011,846 B2	3/2006	Shojaei et al.	8,222,008 B2	7/2012	Thoenne
7,018,992 B2	3/2006	Koch et al.	8,227,454 B2	7/2012	Hill et al.
7,030,157 B2	4/2006	Ke et al.	8,227,509 B2	7/2012	Castro et al.
RE39,104 E	5/2006	Duclos et al.	8,241,664 B2	8/2012	Dudley et al.
7,074,779 B2	7/2006	Sui et al.	8,247,393 B2	8/2012	Ahmed et al.
7,083,590 B1	8/2006	Bunt et al.	8,273,730 B2	9/2012	Fernandez et al.
7,091,213 B2	8/2006	Metcalf, III et al.	8,287,888 B2	10/2012	Song et al.
7,101,342 B1	9/2006	Caillouette	8,329,680 B2	12/2012	Evans et al.
7,135,190 B2	11/2006	Piao et al.	8,349,820 B2	1/2013	Zeun et al.
7,163,681 B2	1/2007	Giles-Komar et al.	8,435,561 B2	5/2013	Besins et al.
7,163,699 B2	1/2007	Besse	2001/0005728 A1	6/2001	Guittard et al.
7,179,799 B2	2/2007	Hill et al.	2001/0021816 A1	9/2001	Caillouette
7,196,074 B2	3/2007	Blye et al.	2001/0027189 A1	10/2001	Bennink et al.
7,198,801 B2	4/2007	Carrara et al.	2001/0029357 A1	10/2001	Bunt et al.
7,226,910 B2	6/2007	Wilson et al.	2001/0031747 A1	10/2001	deZiegler et al.
7,247,625 B2	7/2007	Zhang et al.	2001/0034340 A1	10/2001	Pickar
7,250,446 B2	7/2007	Sangita et al.	2001/0056068 A1	12/2001	Chwalisz et al.
7,300,926 B2	11/2007	Prokai et al.	2002/0012710 A1	1/2002	Lansky
7,303,763 B2	12/2007	Ho	2002/0026158 A1	2/2002	Rathbone et al.
7,317,037 B2	1/2008	Fensome et al.	2002/0028788 A1	3/2002	Bunt et al.
7,329,654 B2	2/2008	Kanojia et al.	2002/0058648 A1	5/2002	Hammerly
7,335,650 B2	2/2008	Potter et al.	2002/0058926 A1	5/2002	Rathbone et al.
7,374,779 B2	5/2008	Chen et al.	2002/0076441 A1	6/2002	Shih et al.
7,378,404 B2	5/2008	Peters et al.	2002/0102308 A1	8/2002	Wei et al.
7,387,789 B2	6/2008	Klose et al.	2002/0107230 A1	8/2002	Waldon et al.
7,388,006 B2	6/2008	Schmees et al.	2002/0114803 A1	8/2002	Deaver et al.
7,414,043 B2	8/2008	Kosemund et al.	2002/0132801 A1	9/2002	Heil et al.
7,427,413 B2	9/2008	Savoir et al.	2002/0137749 A1	9/2002	Levinson et al.
7,427,609 B2	9/2008	Leonard	2002/0151530 A1	10/2002	Leonard et al.
7,429,576 B2	9/2008	Labrie	2002/0156394 A1	10/2002	Mehrotra et al.
7,431,941 B2	10/2008	Besins et al.	2002/0169150 A1	11/2002	Pickar
7,459,445 B2	12/2008	Hill et al.	2002/0173510 A1	11/2002	Levinson et al.
7,465,587 B2	12/2008	Imrich	2002/0193356 A1	12/2002	Van Beek et al.
7,470,433 B2	12/2008	Carrara et al.	2003/0004145 A1	1/2003	Leonard
7,485,666 B2	2/2009	Villanueva et al.	2003/0007994 A1	1/2003	Bunt et al.
7,497,855 B2	3/2009	Ausiello et al.	2003/0049307 A1	3/2003	Gyurik
7,534,765 B2	5/2009	Gregg et al.	2003/0064097 A1	4/2003	Patel et al.
7,550,142 B2	6/2009	Giles-Komar et al.	2003/0072760 A1	4/2003	Sirbasku
7,563,565 B1	7/2009	Matsuo et al.	2003/0073248 A1	4/2003	Roth et al.
7,572,779 B2	8/2009	Aloba et al.	2003/0073673 A1	4/2003	Hesch
7,589,082 B2	9/2009	Savoir et al.	2003/0077297 A1 *	4/2003	Chen et al. .... 424/400
7,671,027 B2	3/2010	Loumaye	2003/0078245 A1	4/2003	Bennink et al.
7,674,783 B2	3/2010	Hermesmyer	2003/0091640 A1	5/2003	Ramanathan et al.
7,687,281 B2	3/2010	Roth et al.	2003/0092691 A1	5/2003	Besse et al.
7,687,485 B2	3/2010	Levinson et al.	2003/0096012 A1	5/2003	Besse et al.
7,694,683 B2	4/2010	Callister et al.	2003/0104048 A1	6/2003	Patel et al.
7,704,983 B1	4/2010	Hodgen et al.	2003/0114420 A1	6/2003	Salvati et al.
			2003/0124182 A1	7/2003	Shojaei et al.
			2003/0124191 A1	7/2003	Besse et al.
			2003/0130558 A1	7/2003	Massara et al.
			2003/0144258 A1	7/2003	Heil et al.

## US 8,633,178 B2

Page 4

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2003/0157157	A1	8/2003	Luo et al.	2006/0020002	A1	1/2006	Salvati et al.
2003/0166509	A1	9/2003	Edwards et al.	2006/0030615	A1	2/2006	Fensome et al.
2003/0180352	A1	9/2003	Patel et al.	2006/0051391	A1	3/2006	Dvoskin et al.
2003/0181353	A1	9/2003	Nyce	2006/0052341	A1	3/2006	Cornish et al.
2003/0181728	A1	9/2003	Salvati et al.	2006/0069031	A1	3/2006	Loumaye
2003/0191096	A1	10/2003	Leonard et al.	2006/0083778	A1	4/2006	Allison et al.
2003/0195177	A1	10/2003	Leonard et al.	2006/0089337	A1	4/2006	Casper et al.
2003/0215496	A1	11/2003	Patel et al.	2006/0093678	A1	5/2006	Chickering, III et al.
2003/0220297	A1	11/2003	Berstein et al.	2006/0106004	A1	5/2006	Brody et al.
2003/0224057	A1	12/2003	Martin-Letellier et al.	2006/0111424	A1	5/2006	Salvati et al.
2003/0224059	A1	12/2003	Lerner et al.	2006/0121626	A1	6/2006	Imrich
2003/0225050	A1*	12/2003	Grawe et al. .... 514/179	2006/0135619	A1	6/2006	Kick et al.
2003/0228686	A1	12/2003	Klausner et al.	2006/0194775	A1	8/2006	Tofovic et al.
2003/0229057	A1	12/2003	Caubel et al.	2006/0204557	A1	9/2006	Gupta et al.
2004/0009960	A1	1/2004	Heil et al.	2006/0235037	A1	10/2006	Purandare et al.
2004/0034001	A1	2/2004	Karara	2006/0240111	A1	10/2006	Fernandez et al.
2004/0037881	A1	2/2004	Guittard et al.	2006/0247216	A1	11/2006	Haj-Yehia
2004/0043943	A1	3/2004	Guittard et al.	2006/0252049	A1	11/2006	Shuler et al.
2004/0044080	A1	3/2004	Place et al.	2006/0257472	A1	11/2006	Nielsen
2004/0073024	A1	4/2004	Metcalf, III et al.	2006/0275360	A1	12/2006	Ahmed et al.
2004/0077605	A1	4/2004	Salvati et al.	2006/0280771	A1	12/2006	Groenewegen et al.
2004/0077606	A1	4/2004	Salvati et al.	2006/0280797	A1	12/2006	Shoichet et al.
2004/0087548	A1	5/2004	Salvati et al.	2006/0280800	A1	12/2006	Nagi et al.
2004/0089308	A1	5/2004	Welch	2007/0004693	A1	1/2007	Woolfson et al.
2004/0092583	A1	5/2004	Shanahan-Prendergast	2007/0004694	A1	1/2007	Woolfson et al.
2004/0097468	A1	5/2004	Wimalawansa	2007/0021360	A1	1/2007	Nyce et al.
2004/0101557	A1	5/2004	Gibson et al.	2007/0027201	A1	2/2007	McComas et al.
2004/0106542	A1	6/2004	Deaver et al.	2007/0031491	A1	2/2007	Levine et al.
2004/0131670	A1	7/2004	Gao	2007/0042038	A1	2/2007	Besse
2004/0142012	A1	7/2004	Bunt et al.	2007/0066628	A1	3/2007	Zhang et al.
2004/0146894	A1	7/2004	Warrington et al.	2007/0066637	A1	3/2007	Zhang et al.
2004/0176324	A1	9/2004	Salvati et al.	2007/0066675	A1	3/2007	Zhang et al.
2004/0176336	A1	9/2004	Rodriguez	2007/0093548	A1	4/2007	Diffendal et al.
2004/0185104	A1	9/2004	Piao et al.	2007/0116729	A1	5/2007	Palepu
2004/0191276	A1	9/2004	Muni	2007/0116829	A1	5/2007	Prakash et al.
2004/0198706	A1	10/2004	Carrara et al.	2007/0178166	A1	8/2007	Bernstein et al.
2004/0213744	A1	10/2004	Lulla et al.	2007/0184558	A1	8/2007	Roth et al.
2004/0234606	A1	11/2004	Levine et al.	2007/0191319	A1	8/2007	Ke et al.
2004/0253319	A1	12/2004	Netke et al.	2007/0196433	A1	8/2007	Ron et al.
2004/0259817	A1	12/2004	Waldon et al.	2007/0207225	A1	9/2007	Squadrito
2004/0266745	A1	12/2004	Schwanitz et al.	2007/0225281	A1	9/2007	Zhang et al.
2005/0004088	A1	1/2005	Hesch	2007/0238713	A1	10/2007	Gast et al.
2005/0009800	A1	1/2005	Thumbek et al.	2007/0243229	A1	10/2007	Smith et al.
2005/0020552	A1	1/2005	Aschkenasy et al.	2007/0264309	A1	11/2007	Chollet et al.
2005/0021009	A1	1/2005	Massara et al.	2007/0264345	A1	11/2007	Eros et al.
2005/0025833	A1	2/2005	Aschkenasy et al.	2007/0286819	A1	12/2007	DeVries et al.
2005/0031651	A1	2/2005	Gervais et al.	2007/0292387	A1	12/2007	Jon et al.
2005/0042173	A1	2/2005	Besse et al.	2008/0026035	A1	1/2008	Chollet et al.
2005/0048116	A1	3/2005	Straub et al.	2008/0026062	A1	1/2008	Farr et al.
2005/0079138	A1	4/2005	Chickering, III et al.	2008/0038350	A1	2/2008	Gerecke et al.
2005/0085453	A1	4/2005	Govindarajan	2008/0085877	A1	4/2008	Bortz
2005/0101579	A1	5/2005	Shippen	2008/0095838	A1	4/2008	Abou Chacra-Vernet
2005/0113350	A1	5/2005	Duesterberg et al.	2008/0113953	A1	5/2008	De Vries et al.
2005/0118272	A1	6/2005	Besse et al.	2008/0114050	A1	5/2008	Fensome et al.
2005/0153946	A1	7/2005	Hirsh et al.	2008/0119537	A1	5/2008	Zhang et al.
2005/0164977	A1	7/2005	Coelingh Bennink	2008/0125402	A1	5/2008	Diliberti
2005/0182105	A1	8/2005	Nirschl et al.	2008/0138379	A1	6/2008	Jennings-Spring
2005/0187267	A1	8/2005	Hamann et al.	2008/0145423	A1	6/2008	Khan et al.
2005/0192253	A1	9/2005	Salvati et al.	2008/0188829	A1	8/2008	Creasy
2005/0192310	A1	9/2005	Gavai et al.	2008/0206161	A1	8/2008	Tamarkin et al.
2005/0207990	A1	9/2005	Funke et al.	2008/0220069	A1	9/2008	Allison
2005/0214384	A1	9/2005	Juturu et al.	2008/0234199	A1	9/2008	Katamreddy
2005/0220825	A1	10/2005	Funke et al.	2008/0255078	A1	10/2008	Katamreddy
2005/0222106	A1	10/2005	Bracht	2008/0255089	A1	10/2008	Katamreddy
2005/0244522	A1	11/2005	Carrara et al.	2008/0299220	A1	12/2008	Tamarkin et al.
2005/0245902	A1	11/2005	Cornish et al.	2008/0312197	A1	12/2008	Rodriguez
2005/0250746	A1	11/2005	Iammatteo	2008/0312198	A1	12/2008	Rodriguez
2005/0250750	A1	11/2005	Cummings et al.	2009/0060982	A1	3/2009	Ron et al.
2005/0250753	A1	11/2005	Fink et al.	2009/0068118	A1	3/2009	Eini et al.
2005/0256028	A1	11/2005	Yun et al.	2009/0081278	A1	3/2009	De Graaff et al.
2005/0266078	A1	12/2005	Jorda et al.	2009/0081303	A1	3/2009	Savoir et al.
2005/0272712	A1	12/2005	Grubb et al.	2009/0092656	A1	4/2009	Klamerus et al.
2006/0014728	A1	1/2006	Chwalisz et al.	2009/0099106	A1	4/2009	Phiasivongsa et al.
2006/0018937	A1	1/2006	Friedman et al.	2009/0131385	A1	5/2009	Voskuhl
2006/0019978	A1	1/2006	Balog	2009/0137478	A1	5/2009	Bernstein et al.
				2009/0137538	A1	5/2009	Klamerus et al.
				2009/0143344	A1	6/2009	Chang
				2009/0181088	A1	7/2009	Song et al.
				2009/0214474	A1	8/2009	Jennings



## US 8,633,178 B2

Page 5

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2009/0227025 A1 9/2009 Nichols et al.  
 2009/0232897 A1 9/2009 Sahoo et al.  
 2009/0258096 A1 10/2009 Cohen  
 2009/0264395 A1 10/2009 Creasy  
 2009/0269403 A1 10/2009 Shaked et al.  
 2009/0285772 A1 11/2009 Phiasivongsa et al.  
 2009/0325916 A1 12/2009 Zhang et al.  
 2010/0028360 A1 2/2010 Atwood  
 2010/0040671 A1 2/2010 Ahmed et al.  
 2010/0048523 A1 2/2010 Bachman et al.  
 2010/0074959 A1 3/2010 Hansom et al.  
 2010/0086599 A1 4/2010 Huempel et al.  
 2010/0092568 A1 4/2010 Lerner et al.  
 2010/0105071 A1 4/2010 Laufer et al.  
 2010/0129320 A1 5/2010 Phiasivongsa et al.  
 2010/0136105 A1 6/2010 Chen et al.  
 2010/0137265 A1 6/2010 Leonard  
 2010/0137271 A1 6/2010 Chen et al.  
 2010/0152144 A1 6/2010 Hermesmeyer  
 2010/0168228 A1 7/2010 Bose et al.  
 2010/0183723 A1 7/2010 Laurent-Applegate et al.  
 2010/0184736 A1 7/2010 Coelingh Bennink et al.  
 2010/0190758 A1 7/2010 Fauser et al.  
 2010/0240626 A1 9/2010 Kulkarni et al.  
 2010/0255085 A1 10/2010 Liu et al.  
 2010/0303825 A9 12/2010 Sirbasku  
 2010/0312137 A1 12/2010 Gilmour et al.  
 2010/0316724 A1 12/2010 Whitfield et al.  
 2010/0330168 A1 12/2010 Gicquel et al.  
 2011/0028439 A1 2/2011 Witt-Enderby et al.  
 2011/0053845 A1 3/2011 Levine et al.  
 2011/0076775 A1 3/2011 Stewart et al.  
 2011/0076776 A1 3/2011 Stewart et al.  
 2011/0086825 A1 4/2011 Chatroux  
 2011/0091555 A1 4/2011 De Luigi Bruschi et al.  
 2011/0098631 A1 4/2011 McIntyre et al.  
 2011/0104289 A1 5/2011 Savoir Vilboeuf et al.  
 2011/0135719 A1 6/2011 Besins et al.  
 2011/0182997 A1 7/2011 Lewis et al.  
 2011/0195114 A1 8/2011 Carrara et al.  
 2011/0195944 A1 8/2011 Mura et al.  
 2011/0217341 A1 9/2011 Sah  
 2011/0250274 A1 10/2011 Shaked et al.  
 2011/0256092 A1 10/2011 Phiasivongsa et al.  
 2011/0262494 A1 10/2011 Achleitner et al.  
 2011/0268665 A1 11/2011 Tamarkin et al.  
 2011/0293720 A1 12/2011 General et al.  
 2011/0311592 A1 12/2011 Birbara  
 2011/0312927 A1 12/2011 Nachaegari et al.  
 2011/0312928 A1 12/2011 Nachaegari et al.  
 2012/0009276 A1 1/2012 De Groote  
 2012/0015350 A1 1/2012 Nabatiyan et al.  
 2012/0045532 A1 2/2012 Cohen  
 2012/0052077 A1 3/2012 Truitt, III et al.  
 2012/0128625 A1 5/2012 Shalwitz et al.  
 2012/0128777 A1 5/2012 Keck et al.  
 2012/0149748 A1 6/2012 Shanler et al.  
 2012/0269721 A1 10/2012 Weng et al.  
 2012/0269878 A2 10/2012 Cantor et al.  
 2012/0283671 A1 11/2012 Shibata et al.  
 2013/0022674 A1 1/2013 Dudley et al.  
 2013/0029947 A1 1/2013 Nachaegari et al.  
 2013/0129818 A1 5/2013 Bernick et al.

## FOREIGN PATENT DOCUMENTS

IN 216026 3/2008  
 IN 2005KO00053 9/2009  
 IN 244217 11/2010  
 WO 9011064 A1 10/1990  
 WO 9317686 A1 9/1993  
 WO 9422426 A1 3/1994  
 WO 9530409 A1 11/1995  
 WO 9609826 A2 4/1996

WO 9630000 A1 10/1996  
 WO 9743989 A1 11/1997  
 WO 9810293 A1 3/1998  
 WO 9832465 A1 7/1998  
 WO 9851280 A1 11/1998  
 WO 9939700 A1 2/1999  
 WO 9932072 A1 7/1999  
 WO 9942109 A1 8/1999  
 WO 9948477 A1 9/1999  
 WO 9553910 A2 10/1999  
 WO 0038659 A1 11/1999  
 WO 9963974 A2 12/1999  
 WO 0006175 A1 2/2000  
 WO 0045795 A2 8/2000  
 WO 0050007 A1 8/2000  
 WO 0059577 A1 10/2000  
 WO 0137808 A1 11/2000  
 WO 0076522 A1 12/2000  
 WO 0154699 A1 8/2001  
 WO 0160325 A1 8/2001  
 WO 0207700 A2 1/2002  
 WO 0211768 A1 2/2002  
 WO 0222132 A2 3/2002  
 WO 0240008 A2 5/2002  
 WO 02053131 A1 7/2002  
 WO 03041718 A1 5/2003  
 WO 03041741 A1 5/2003  
 WO 03068186 A1 8/2003  
 WO 03082254 A1 10/2003  
 WO 03092588 A2 11/2003  
 WO 2004017983 A1 3/2004  
 WO 2005027911 A1 3/2004  
 WO 2004032897 A2 4/2004  
 WO 2004052336 A2 6/2004  
 WO 2005120517 A1 6/2004  
 WO 2004054540 A2 7/2004  
 WO 2004080413 A2 9/2004  
 WO 2005030175 A1 4/2005  
 WO 2005087194 A1 9/2005  
 WO 2005087199 A2 9/2005  
 WO 2005105059 A1 11/2005  
 WO 2005115335 A1 12/2005  
 WO 2005120470 A1 12/2005  
 WO 2006013369 A2 2/2006  
 WO 2006034090 A1 3/2006  
 WO 2006036899 A2 4/2006  
 WO 2006053172 A2 5/2006  
 WO 2006105615 A1 10/2006  
 WO 2006113505 A2 10/2006  
 WO 2006138686 A1 12/2006  
 WO 2006138735 A2 12/2006  
 WO 2007045027 A1 4/2007  
 WO 2007103294 A2 9/2007  
 WO 2007123790 A1 11/2007  
 WO 2007124250 A2 11/2007  
 WO 2007144151 A1 12/2007  
 WO 2008049516 A3 5/2008  
 WO 2008152444 A2 12/2008  
 WO 2009002542 A1 12/2008  
 WO 2009036311 A1 3/2009  
 WO 2009069006 A2 6/2009  
 WO 2009098072 A2 8/2009  
 WO 2009133352 A2 11/2009  
 WO 2010033188 A2 3/2010  
 WO 2011000210 A1 1/2011  
 WO 2011073995 A2 6/2011  
 WO 2011120084 A1 10/2011  
 WO 2011128336 A1 10/2011  
 WO 2012009778 A2 1/2012  
 WO 2012024361 A1 2/2012

## OTHER PUBLICATIONS

Azure Pharma, Inc., "Elestrin™—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages, 2009.  
 Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," J. Kor. Pharm. Sci., 35(3):173-177, 2005.

## US 8,633,178 B2

Page 6

(56)

## References Cited

## OTHER PUBLICATIONS

- Committee of Obstetric Practice, Committee Opinion—No. 522, *Obstetrics & Gynecology*, 119(4):879-882, 2012.
- Diramio, "Polyethylene Glycol Methacrylate/Dimetacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia—Masters of Science Thesis, 131 pages, 2004. [http://athenaeum.libs.uga.edu/bitstream/handle/10724/7820/diramio\\_jackie\\_a\\_200412\\_ms.pdf?sequence=1](http://athenaeum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1).
- Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," *International Journal of Pharmaceutics*, 147(2):165-171, 1997. Abstract Only.
- Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," *Critical Reviews in Toxicology*, 30(3):307-345, 2000. Abstract Only.
- Knuth et al., "Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations," *Advanced Drug Delivery Reviews*, 11(1-2):137-167, 1993. Abstract Only.
- Lucy et al., "Gonadotropin-releasing hormone at estrus: luteinizing hormone, estradiol, and progesterone during the periestrual and postinsemination periods in dairy cattle," *Biol Reprod.*, 35(2):300-11, 1986. Abstract Only.
- NuGen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, 3 pages, undated.
- NuGest 900™, <http://www.thehormoneshop.net/nugest900.htm>, 4 pages, undated.
- Panchagnula et al., "Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol as a cosolvent: in-vitro, ex-vivo and in-vivo rat studies," *J Pharm Pharmacol.*, 43(9):609-14, 1991. Abstract Only.
- Salole, "The physicochemical properties of oestradiol," *Journal of Pharmaceutical & Biomedical Analysis*, 5(7):635-648, 1987.
- Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," *Pharmaceutical Research*, 21(2):201-230, 2004.
- Tahitian Noni, "Body Balance Cream," [http://products.tni.com/dominican\\_republic/sa\\_spanish/nonistore/product/3438/3416/](http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/), 1 page, undated.
- Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," *Skin Pharmacol Physiol.*, 19:106-121, 2006. [http://www.nanobiotec.iqm.unicamp.br/download/Trommer\\_skin%20penetration-2006rev.pdf](http://www.nanobiotec.iqm.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf).
- International Search report for corresponding International Application No. PCT/US12/66406, mailed Jan. 24, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/023309 mailed Apr. 9, 2013.
- Acarturk, "Mucoadhesive Vaginal Drug Delivery System," *Recent Patents on Drug Delivery & Formulation*, 3 (3):193-205, 2009.
- Fuchs et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," *Aesthetic Dermatology*, 8(1):14-19, 2006.
- Panay et al., "The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy," DOI: 0.1177/1754045313489645, [min.sagepub.com](http://min.sagepub.com). *Menopause International: The Integrated Journal of Postreproductive Health* 0(0):1-10, 2013.
- Bhavnani et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," *J Clin Endocrinol Metab.* doi:10.1210/jc.2011-2492, 97(3):0000-0000, 2011, 4 pages.
- Bhavnani et al., "Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ER $\alpha$  and ER $\beta$ ," *Endocrinology* 2008;149(10):4857-4870.
- Du et al., "Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood," *Menopause: The Journal of the North American Menopause Society*, doi: 10.1097/gme.0b013e31828d39a2, 20(11):0000-0000, 2013, 7 pages.
- Hargrove et al., "Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronize Estradiol and Progesterone," *Obstetrics & Gynecology: Estrogen Replacement Therapy* 1989;73(4):606-612.
- Patel et al., "Transdermal Drug Delivery System: A Review," *The Pharma Innovation* 2012;1(4):78-87.
- Sarrel et al., "The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years," *American Journal of Public Health, Research and Practice*, e1-e6. doi:10.2105/AJPH.2013.301295, 2013.
- Sitruk-Ware, "Progestogens in hormonal replacement therapy: new molecules, risks, and benefits," *Menopause: The Journal of The North American Menopause Society* 2002;9(1):6-15.
- Stanczyk et al., "Ethinyl estradiol and 17 $\beta$ -estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment," *Elsevier* 2013;87:706-727.
- Wood et al., "Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys," *Breast Cancer Res Treat* 2007;101:125-134.
- Fotherby, "Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy," *Elsevier* 1996;54:59-69.
- Kincl et al., "Increasing Oral Bioavailability of Progesterone by Formulation," *Journal of Steroid Biochemistry* 1978;9:83-84.
- NAMS "Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society," *Menopause: The Journal of the North American Menopause Society* 2013;20(9):888-902.
- Sitruk-Ware et al., "Oral Micronized Progesterone—Bioavailability pharmacokinetics, pharmacological and therapeutic implications—A review," *Contraception* 1987;36(4):373-402.
- Shufelt et al., "Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study," *Menopause: The Journal of The North American Menopause Society* 2013;DOI: 10.1097/GME.0b013e31829a64f9:1-7.
- Smith et al., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens," *JAMA Internal Medicine* 2013;doi:10.1001/jamainternmed.2013.11074:E1-E7.
- Whitehead et al., "Absorption and metabolism of oral progesterone," *British Medical Journal* 1980;825-827.
- US 6,214,374, 04/2001, Schmirler et al. (withdrawn)

\* cited by examiner

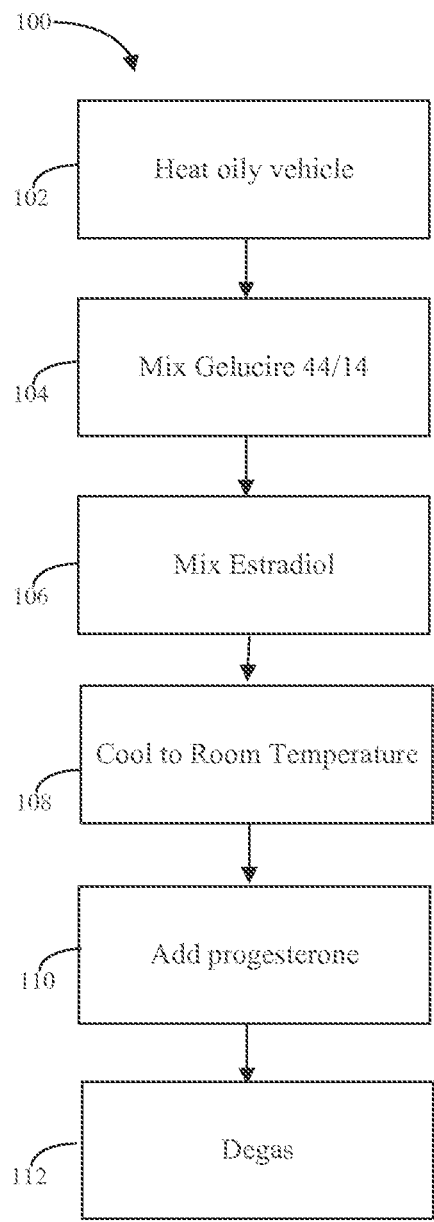


Fig. 1

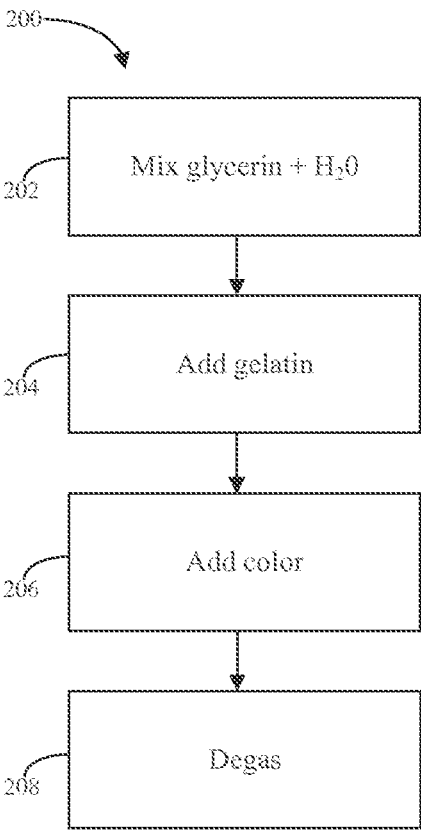


Fig. 2

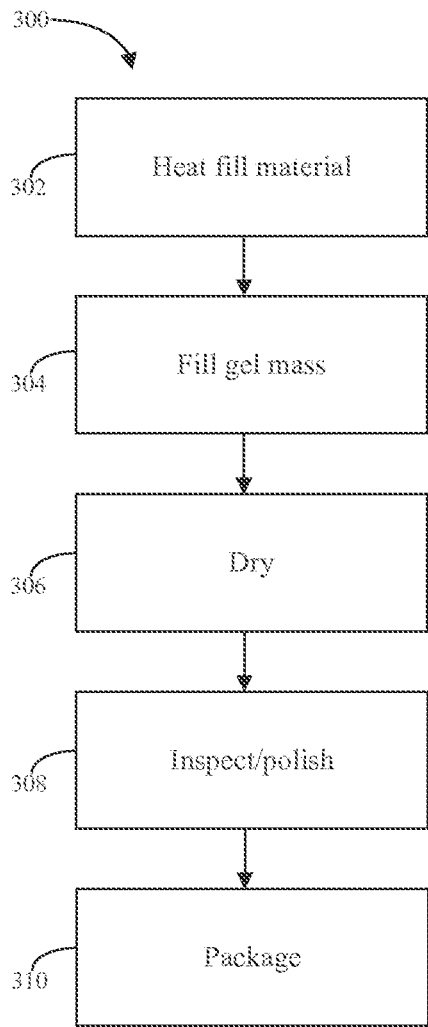


Fig. 3

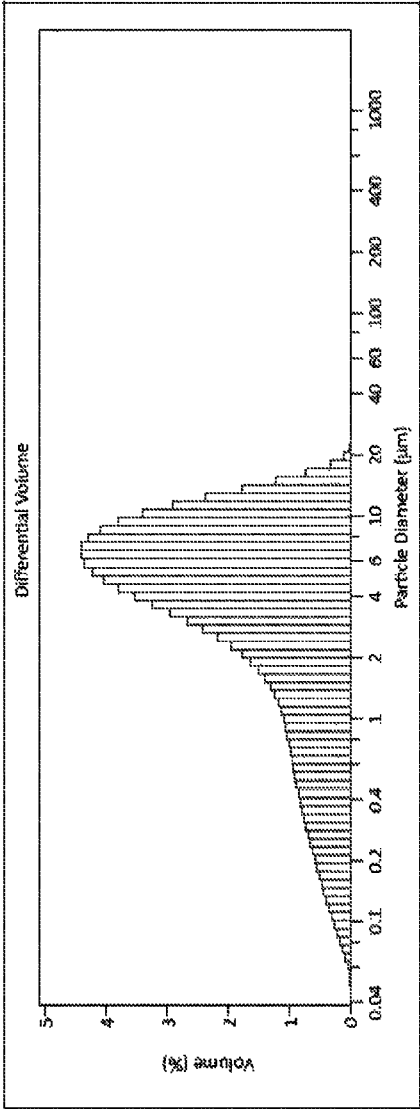


FIG. 4

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## NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

### CROSS REFERENCE TO RELATED APPLICATIONS

This application is a nonprovisional application of and claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and 3. U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

### BACKGROUND

#### 1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

#### 2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

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"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as PREM-PRO (conjugated estrogens/medroxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens plus medroxyprogesterone acetate tablets) (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN (conjugated estrogens tablets) (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

### SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

### BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

### DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because



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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

#### DEFINITIONS

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to PROMETRIUM (progesterone, USP) at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC,  $C_{max}$ , and optionally,  $T_{max}$ .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ $C_{max}$ ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ $T_{max}$ ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC,  $C_{max}$  and, optionally,  $T_{max}$  are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to estab-

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lished governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

#### Description

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM (progesterone, USP) when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of



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progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of PROMETRIUM (progesterone, USP). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM (progesterone, USP) equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM (progesterone, USP) can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 $\beta$ -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125,

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1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017  $\mu$ m to 2000  $\mu$ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4  $\mu$ m to 2000  $\mu$ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

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Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE (a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride); SASOL Germany GMBH, Hamburg; MIGLYOL (caprylic/capric triglyceride) includes MIGLYOL 810 (Caprylic/Capric Triglyceride), MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 816 (Caprylic/Capric Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL PG-10 (Propylene Glycol Monocaprate); the CAPMUL brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM (Medium Chain Mono- and Diglycerides)); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL (diethylene glycol mono ester)); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL (caprylic/capric triglyceride); TRANSCUTOL (Diethylene glycol monoethyl ether), MIGLYOL (caprylic/capric triglyceride) and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant; and CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for full solubilization of progesterone. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride) can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone

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per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

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As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the com-

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monly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

## EXAMPLES

### Example 1

#### Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL HP	141
(Highly purified diethylene glycol monoethyl ether EP/NF)	
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	31.2

\*Literature reference—Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

### Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) at 50%; and also CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL PG-8 (Propylene Glycol Monocaprylate) mixed with MIGLYOL (caprylic/capric triglyceride) at the 15 and 30% level did not provide sufficient solubility.

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TABLE 2

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (85:15)	4.40
MIGLYOL (caprylic/capric triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	8.60
TRANSCUTOL (Diethylene glycol monoethyl ether) MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	>12
TRANSCUTOL (Diethylene glycol monoethyl ether) MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	>12
MIGLYOL (caprylic/capric triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	14.0
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	19.8
polysorbate 80: CAPMUL MCM (Medium Chain Mono- and Diglycerides) (20:80)	15.0

## Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. MIGLYOL 812 (Caprylic/Capric Triglyceride) with 4% TRANSCUTOL (Diethylene glycol monoethyl ether) precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL (caprylic/capric triglyceride): CAPMUL (a propylene glycol monocaprylate; propylene glycol monocaprylate) blends at 30 and 50% or in CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
TRANSCUTOL (Diethylene glycol monoethyl ether) MIGLYOL 812 (Caprylic/Capric Triglyceride) (4:96)	4	Crystallizes after 96 hours
MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	6	Clear, after 14 days
TRANSCUTOL (Diethylene glycol monoethyl ether) MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	6	Clear, after 14 days
CAPMUL MCM(Medium Chain Mono- and Diglycerides)	6	Clear, after 14 days

12 mg estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) 50:50, CAPMUL MCM (Medium Chain Mono- and Diglycerides), and in mixtures of TRANSCUTOL (Diethyl-

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ene glycol monoethyl ether):MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether) MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	12	Clear, after 12 days
CAPMUL MCM(Medium Chain Mono- and Diglycerides)	12	Clear, after 12 days

## Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization. All CAPMUL PG-8 (Propylene Glycol Monocaprylate) containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL PG-8 (Propylene Glycol Monocaprylate) alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25)	6	Precipitated
MIGLYOL 812 (Caprylic/Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Hazy



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TABLE 5-continued

Formulation	Estradiol mg/g	Results after addition of 7% water
TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL 812 (Caprylic/ Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28) CAPMUL MCM(Medium Chain Mono- and Diglycerides)	12	Hazy
TRANSCUTOL (Diethylene glycol monoethyl ether) MIGLYOL 812 (Caprylic/ Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Clear
TRANSCUTOL (Diethylene glycol monoethyl ether) MIGLYOL 812 (Caprylic/ Capric Triglyceride): CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Hazy

## Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (TRANSCUTOL HP) (Highly purified diethylene glycol monoethyl ether EP/NF)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

## Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM) (Medium Chain Mono- and Diglycerides)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

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In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM) (Medium Chain Mono- and Diglycerides)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved.

## Example 7

## Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL (caprylic/capric triglyceride) was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL (caprylic/capric triglyceride) may be used in embodiments comprising a suspension of progesterone, though MIGLYOL (caprylic/capric triglyceride), standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM (Medium Chain Mono- and Diglycerides) is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL (caprylic/capric triglyceride) had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL MCM (Medium Chain Mono- and Diglycerides). It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL MCM (Medium Chain Mono- and Diglycerides).

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TABLE 9

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	73.4
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	95
MIGLYOL 812 (Caprylic/Capric Triglyceride)	27.8

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM (Medium Chain Mono- and Diglycerides) in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Gelucire 44/14 system, wherein the ratio of CAPMUL MCM (Medium Chain Mono- and Diglycerides) to GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides): GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG) (9:1))	86.4
CAPMUL MCM (Medium Chain Mono- and Diglycerides): GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG) (7:3))	70.5
CAPMUL MCM (Medium Chain Mono- and Diglycerides): GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (6:4)	57.4

## Example 7

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97
GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this

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Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL MCM (Medium Chain Mono- and Diglycerides) may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/- 2° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) may be added to the CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Heat may be removed from the GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

## Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 Caprylic/Capric Triglyceride) or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL (caprylic/capric triglyceride) MIGLYOL is heated to about 45° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

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TABLE 13

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/ diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM) (Medium Chain Mono- and Diglycerides)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32 glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to about 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride MIGLYOL 812 (Caprylic/ Capric Triglyceride) or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32 glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	300	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL (caprylic/capric triglyceride) may be present in a range from about 35-95% by weight; GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API com-

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prising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

## Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 µm, an X75 of 17.3 µm, and an X25 of 5.3 µm. The Beckman Device also yielded that the mean particle size is 11.8 µm, the median particle size is 11.04 µm, the mode particle size is 13.6 µm, and the standard deviation is 7.8 µm.

## Example 12

In order to increase the solubility of progesterone in the final solution, GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97	5.78
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 40° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

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## Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		73.371	146.74	1467.42
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.500	3.00	30.00
Total:			100.000	200.00 mg	2000.00

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		65.32	391.93	3919.3
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

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## Example 15

### Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM (progesterone, USP) (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM (progesterone, USP) soft gel Capsule 200 mg and ESTRACE (estradiol vaginal cream, USP, 0.01%) ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.



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All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of  $-70^{\circ}\text{C} \pm 20^{\circ}\text{C}$  in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

## Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to  $40^{\circ}\text{C} \pm 5^{\circ}\text{C}$ . Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ .

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any

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suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Heating may be performed until the temperature reaches  $80^{\circ}\text{C} \pm 5^{\circ}\text{C}$ .

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to  $30^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes. Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of  $55^{\circ}\text{C} \pm 10^{\circ}\text{C}$ . The wedge temperature may be  $38^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . The drum cooling temperature may be  $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$ . The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness  $0.85\text{ mm} \pm 0.05\text{ mm}$  using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight  $\pm 5\%$  (i.e.,  $650 \pm 33\text{ mg}$  and  $325 \pm 16.3\text{ mg}$ ).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A pharmaceutical formulation comprising solubilized estradiol, suspended progesterone, and a medium chain solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed;

wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises a C6-C12 oil.

2. The pharmaceutical formulation of claim 1, further comprising partially solubilized progesterone.

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3. The pharmaceutical formulation of claim 1, wherein the formulation is contained within a gelatin capsule.

4. The pharmaceutical formulation of claim 1, wherein the medium chain solubilizing agent is selected from at least one of mono-, di-, and triglycerides and combinations thereof. 5

5. The pharmaceutical formulation of claim 1, wherein said estrogen has a dosage strength at least about 0.125 mg and wherein said progesterone has a dosage strength at least about 25 mg.

6. The pharmaceutical formulation of claim 1, wherein the 10 ratio of progesterone to estradiol is at least 95:1.

\* \* \* \* \*

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UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,633,178 B2  
APPLICATION NO. : 13/684002  
DATED : January 21, 2014  
INVENTOR(S) : Brian A. Bernick et al.

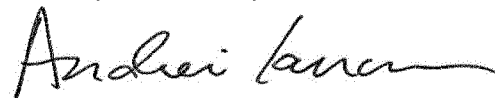
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this  
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu  
*Director of the United States Patent and Trademark Office*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,633,178 B2  
APPLICATION NO. : 13/684002  
DATED : January 21, 2014  
INVENTOR(S) : Brian A. Bernick et al.

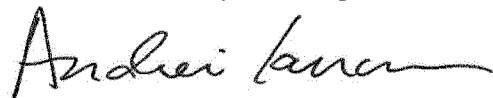
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 23, Claim 5, Line 7: Delete “estrogen” and insert in its place --estradiol--.

Signed and Sealed this  
Twentieth Day of August, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu  
*Director of the United States Patent and Trademark Office*

# **EXHIBIT B**



US008846648B2

(12) **United States Patent**  
**Bernick et al.**

(10) **Patent No.:** **US 8,846,648 B2**  
(45) **Date of Patent:** **\*Sep. 30, 2014**

(54) **NATURAL COMBINATION HORMONE  
REPLACEMENT FORMULATIONS AND  
THERAPIES**

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(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.  
  
This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/099,545**

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(65) **Prior Publication Data**

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(60) Provisional application No. 61/662,265, filed on Jun. 20, 2012, provisional application No. 61/661,302, filed on Jun. 18, 2012, provisional application No. 61/563,408, filed on Nov. 23, 2011.

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USPC ..... 514/169  
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(56) **References Cited**

**U.S. PATENT DOCUMENTS**

1,967,351 A 7/1934 Doisy  
2,379,832 A 7/1945 Serini et al.  
2,649,399 A 8/1953 Grant et al.  
3,198,707 A 8/1965 Nomaine et al.  
3,478,070 A 11/1969 Smith et al.  
3,526,648 A 9/1970 Bertin et al.

3,710,795 A 1/1973 Higuchi et al.  
3,729,560 A 4/1973 Hagerman  
3,729,566 A 4/1973 Ericsson et al.  
3,755,573 A 8/1973 Berman  
3,755,575 A 8/1973 Lerner  
3,903,880 A 9/1975 Higuchi et al.  
3,916,898 A 11/1975 Robinson  
3,916,899 A 11/1975 Higuchi et al.  
3,921,636 A 11/1975 Zaffaroni  
3,923,997 A 12/1975 Meuly  
3,948,254 A 4/1976 Zaffaroni  
3,971,367 A 7/1976 Zaffaroni  
3,977,404 A 8/1976 Theeuwes  
3,993,072 A 11/1976 Zaffaroni  
4,008,719 A 2/1977 Theeuwes  
4,012,496 A 3/1977 Hartmann et al.  
4,014,334 A 3/1977 Theeuwes et al.  
4,014,987 A 3/1977 Heller et al.  
4,016,251 A 4/1977 Higuchi et al.  
4,071,623 A 1/1978 Van Der Vies  
4,093,709 A 6/1978 Choi  
4,154,820 A 5/1979 Simoons  
4,155,991 A 5/1979 Schopflin et al.  
4,196,188 A 4/1980 Besins  
4,215,691 A 8/1980 Wong  
4,237,885 A 12/1980 Wong  
4,310,510 A 1/1982 Sherman et al.  
4,327,725 A 5/1982 Cortese et al.  
4,372,951 A 2/1983 Vorys  
4,384,096 A 5/1983 Sonnabend

(Continued)

**FOREIGN PATENT DOCUMENTS**

CN 102258455 A 11/2011  
EP 0275716 A1 7/1988  
EP 0622075 A1 11/1994  
EP 0785211 A1 1/1996  
EP 0811381 A1 6/1997

(Continued)

**OTHER PUBLICATIONS**

Chempro, "Fatty Acid Composition of Some Major Oils," available at <http://www.chempro.in/fattyacid.htm>, webpage captured on May 26, 2010 (2 total pages).\*

(Continued)

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(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

**20 Claims, 4 Drawing Sheets**

## US 8,846,648 B2

Page 2

(56)

## References Cited

## U.S. PATENT DOCUMENTS

4,393,871	A	7/1983	Vorhauer	5,827,200	A	10/1998	Caillouette
4,402,695	A	9/1983	Wong	5,866,603	A	2/1999	Li et al.
4,423,151	A	12/1983	Baranczuk	5,891,868	A	4/1999	Cummings et al.
4,449,980	A	5/1984	Millar et al.	5,898,038	A	4/1999	Yallampalli et al.
4,610,687	A	9/1986	Fogwell	5,916,176	A	6/1999	Caillouette
4,629,449	A	12/1986	Wong	RE36,247	E	7/1999	Plunkett et al.
4,732,763	A	3/1988	Beck et al.	5,922,349	A	7/1999	Elliesen et al.
4,738,957	A	4/1988	Laurent et al.	5,928,666	A	7/1999	Farinas et al.
4,756,907	A	7/1988	Beck et al.	5,958,446	A	9/1999	Miranda et al.
4,762,717	A	8/1988	Crowley	5,962,445	A	10/1999	Stewart
4,788,062	A	11/1988	Gale et al.	5,972,372	A	10/1999	Saleh et al.
4,816,257	A	3/1989	Buster et al.	5,985,861	A	11/1999	Levine et al.
4,822,616	A	4/1989	Zimmermann et al.	5,993,856	A	11/1999	Ragavan et al.
4,865,848	A	9/1989	Cheng et al.	6,001,846	A	12/1999	Edwards et al.
4,900,734	A *	2/1990	Maxson et al. .... 514/171	6,022,562	A	2/2000	Autant et al.
4,906,475	A	3/1990	Kim	6,024,976	A	2/2000	Miranda et al.
4,942,158	A	7/1990	Sarpotdar et al.	6,028,057	A	2/2000	Burns
4,961,931	A	10/1990	Wong	6,039,968	A	3/2000	Nabahi
5,030,629	A	7/1991	Rajadhyaksha	6,056,972	A	5/2000	Hermesmyer
5,064,654	A	11/1991	Berner et al.	6,060,077	A	5/2000	Meignant
5,108,995	A	4/1992	Casper	6,074,625	A	6/2000	Hawthorne et al.
5,128,138	A	7/1992	Blank	6,077,531	A	6/2000	Salin-Drouin
5,130,137	A	7/1992	Crowley	6,080,118	A	6/2000	Blythe
5,140,021	A	8/1992	Maxson et al.	6,083,178	A	7/2000	Caillouette
5,211,952	A	5/1993	Pike et al.	6,086,916	A	7/2000	Agnus et al.
5,252,334	A	10/1993	Chiang et al.	6,096,338	A	8/2000	Lacy et al.
5,280,023	A	1/1994	Ehrlich et al.	6,117,446	A	9/2000	Place
5,288,496	A	2/1994	Lewis	6,117,450	A	9/2000	Dittgen et al.
5,340,584	A	8/1994	Spicer et al.	6,133,251	A	10/2000	Dittgen et al.
5,340,585	A	8/1994	Pike et al.	6,133,320	A	10/2000	Yallampalli et al.
5,340,586	A	8/1994	Pike et al.	6,139,873	A	10/2000	Hughes, Jr. et al.
5,362,497	A	11/1994	Yamada et al.	6,153,216	A	11/2000	Cordes et al.
5,382,573	A	1/1995	Casper	6,165,491	A	12/2000	Grasset et al.
5,393,528	A	2/1995	Staab	6,165,975	A	12/2000	Adams et al.
5,393,529	A	2/1995	Hoffmann et al.	6,187,339	B1	2/2001	de Haan et al.
5,419,910	A	5/1995	Lewis	6,190,331	B1	2/2001	Caillouette
5,468,736	A	11/1995	Hodgen	6,201,072	B1	3/2001	Rathi et al.
5,474,783	A	12/1995	Miranda et al.	6,227,202	B1	5/2001	Matapurkar
5,480,776	A	1/1996	Dullien	6,262,115	B1	7/2001	Guittard et al.
5,514,673	A	5/1996	Heckenmuller et al.	6,277,418	B1	8/2001	Markaverich et al.
5,516,528	A	5/1996	Hughes et al.	6,283,927	B1	9/2001	Caillouette
5,527,534	A	6/1996	Myhling	6,287,588	B1	9/2001	Shih et al.
5,529,782	A	6/1996	Staab	6,287,693	B1	9/2001	Savoir et al.
5,543,150	A	8/1996	Bologna et al.	6,294,188	B1	9/2001	Ragavan et al.
5,547,948	A	8/1996	Barcomb	6,294,192	B1	9/2001	Patel et al.
5,565,199	A	10/1996	Page et al.	6,294,550	B1	9/2001	Place et al.
5,567,831	A	10/1996	Li	6,299,900	B1	10/2001	Reed et al.
5,569,652	A	10/1996	Beier et al.	6,306,841	B1	10/2001	Place et al.
5,582,592	A	12/1996	Kendrick	6,306,914	B1	10/2001	Ziegler et al.
5,585,370	A	12/1996	Casper	6,309,669	B1	10/2001	Setterstrom et al.
5,595,759	A	1/1997	Wright et al.	6,309,848	B1	10/2001	Howett et al.
5,595,970	A	1/1997	Garfield et al.	6,342,491	B1	1/2002	Dey et al.
5,620,705	A	4/1997	Dong et al.	6,372,209	B1	4/2002	Chrisope
5,629,021	A	5/1997	Wright	6,372,246	B1	4/2002	Wei et al.
5,633,011	A	5/1997	Dong et al.	6,387,390	B1	5/2002	Deaver et al.
5,633,242	A	5/1997	Oettel et al.	6,402,705	B1	6/2002	Caillouette
5,639,743	A	6/1997	Kaswan et al.	6,416,778	B1	7/2002	Ragavan et al.
5,656,286	A	8/1997	Miranda et al.	6,423,039	B1	7/2002	Rathbone et al.
5,676,968	A	10/1997	Lipp et al.	6,423,683	B1	7/2002	Heaton et al.
5,677,292	A	10/1997	Li et al.	6,436,633	B1	8/2002	Kreider et al.
5,694,947	A	12/1997	Lehtinen et al.	6,440,454	B1	8/2002	Santoro et al.
5,709,844	A	1/1998	Arbeit et al.	6,444,224	B1	9/2002	Rathbone et al.
5,735,801	A	4/1998	Caillouette	6,444,234	B1	9/2002	Kirby et al.
5,739,176	A	4/1998	Dunn et al.	6,451,339	B2	9/2002	Patel et al.
5,744,463	A	4/1998	Bair	6,451,779	B1	9/2002	Hesch
5,747,058	A	5/1998	Tipton et al.	6,455,246	B1	9/2002	Howett et al.
5,762,614	A	6/1998	Caillouette	6,455,517	B1	9/2002	Tanabe et al.
5,770,176	A	6/1998	Nargessi	6,468,526	B2	10/2002	Chrisope
5,770,219	A	6/1998	Chiang et al.	6,469,016	B1	10/2002	Place et al.
5,776,495	A	7/1998	Duclos et al.	6,472,434	B1	10/2002	Place et al.
5,788,980	A	8/1998	Nabahi	6,479,232	B1	11/2002	Howett et al.
5,789,442	A	8/1998	Garfield et al.	6,500,814	B1	12/2002	Hesch
5,811,416	A	9/1998	Chwalisz et al.	6,503,896	B1	1/2003	Tanabe et al.
5,811,547	A	9/1998	Nakamichi et al.	6,511,969	B1	1/2003	Hermesmyer
5,814,329	A	9/1998	Shah	6,526,980	B1	3/2003	Tracy et al.
				6,528,094	B1	3/2003	Savoir et al.
				6,537,580	B1	3/2003	Savoir et al.
				6,544,196	B2	4/2003	Caillouette
				6,544,553	B1	4/2003	Hsia et al.

## US 8,846,648 B2

Page 3

(56)

## References Cited

## U.S. PATENT DOCUMENTS

6,548,491 B2	4/2003	Tanabe et al.	7,388,006 B2	6/2008	Schmees et al.
6,551,611 B2	4/2003	Elliesen et al.	7,414,043 B2	8/2008	Kosemund et al.
6,569,463 B2	5/2003	Patel et al.	7,427,413 B2	9/2008	Savoir et al.
6,583,129 B1	6/2003	Mazer et al.	7,427,609 B2	9/2008	Leonard
6,586,006 B2	7/2003	Roser et al.	7,429,576 B2	9/2008	Labrie
6,589,549 B2	7/2003	Shih et al.	7,431,941 B2	10/2008	Besins et al.
6,593,317 B1	7/2003	de Ziegler et al.	7,459,445 B2	12/2008	Hill et al.
6,610,652 B2	8/2003	Adams et al.	7,465,587 B2	12/2008	Imrich
6,610,670 B2	8/2003	Backensfeld et al.	7,470,433 B2	12/2008	Carrara et al.
6,638,536 B2	10/2003	Savoir et al.	7,485,666 B2	2/2009	Villanueva et al.
6,645,528 B1	11/2003	Straub et al.	7,497,855 B2	3/2009	Ausiello et al.
6,653,298 B2	11/2003	Potter et al.	7,534,765 B2	5/2009	Gregg et al.
6,656,929 B1	12/2003	Agnus et al.	7,550,142 B2	6/2009	Giles-Komar et al.
6,660,726 B2	12/2003	Hill et al.	7,563,565 B1	7/2009	Matsuo et al.
6,663,608 B2	12/2003	Rathbone et al.	7,572,779 B2	8/2009	Aloba et al.
6,663,895 B2	12/2003	Savoir et al.	7,572,780 B2	8/2009	Hermismeyer
6,692,763 B1	2/2004	Cummings et al.	7,589,082 B2	9/2009	Savoir et al.
6,737,081 B2	5/2004	Savoir et al.	7,671,027 B2	3/2010	Loumaye
6,740,333 B2	5/2004	Beckett et al.	7,674,783 B2	3/2010	Hermismeyer
6,743,815 B2	6/2004	Navaratnam et al.	7,687,281 B2	3/2010	Roth et al.
6,747,018 B2	6/2004	Tanabe et al.	7,687,485 B2	3/2010	Levinson et al.
6,756,208 B2	6/2004	Griffin et al.	7,694,683 B2	4/2010	Callister et al.
6,776,164 B2	8/2004	Bunt et al.	7,704,983 B1	4/2010	Hodgen et al.
6,787,152 B2	9/2004	Kirby et al.	7,727,720 B2	6/2010	Dhallan
6,805,877 B2	10/2004	Massara et al.	7,732,408 B2	6/2010	Josephson et al.
6,809,085 B1	10/2004	Elson et al.	7,749,989 B2	7/2010	Hill et al.
6,818,226 B2	11/2004	Reed et al.	7,767,656 B2	8/2010	Shoichet et al.
6,841,716 B1	1/2005	Tsutsumi	7,815,949 B2	10/2010	Cohen
6,844,334 B2	1/2005	Hill et al.	7,829,115 B2	11/2010	Besins et al.
6,855,703 B1	2/2005	Hill et al.	RE42,012 E	12/2010	Deaver et al.
6,860,859 B2	3/2005	Mehrotra et al.	7,858,607 B2	12/2010	Manchur
6,866,865 B2	3/2005	Hsia et al.	RE42,072 E	1/2011	Deaver et al.
6,869,969 B2	3/2005	Huebner et al.	7,862,552 B2	1/2011	McIntyre et al.
6,878,518 B2	4/2005	Whitehead	7,867,990 B2	1/2011	Schultz et al.
6,901,278 B1	5/2005	Notelovitz	7,879,830 B2	2/2011	Wiley
6,905,705 B2	6/2005	Palm et al.	7,884,093 B2	2/2011	Creasy et al.
6,911,438 B2	6/2005	Wright	7,939,104 B2	5/2011	Barbera et al.
6,923,988 B2	8/2005	Patel et al.	7,943,602 B2	5/2011	Bunschoten et al.
6,924,274 B2	8/2005	Lardy et al.	7,943,604 B2	5/2011	Coelingh Bennink et al.
6,932,983 B1	8/2005	Straub et al.	7,989,436 B2	8/2011	Hill et al.
6,939,558 B2	9/2005	Massara et al.	7,989,487 B2	8/2011	Welsh et al.
6,943,021 B2	9/2005	Klausner et al.	8,022,053 B2	9/2011	Mueller et al.
6,958,327 B1	10/2005	Hillisch et al.	8,048,869 B2	11/2011	Bunschoten et al.
6,962,691 B1	11/2005	Lulla et al.	8,071,729 B2	12/2011	Giles-Komar et al.
6,962,908 B2	11/2005	Aloba et al.	8,076,319 B2	12/2011	Leonard
6,967,194 B1	11/2005	Matsuo et al.	8,088,605 B2	1/2012	Beaudet et al.
6,977,250 B2	12/2005	Rodriguez	8,101,209 B2	1/2012	Legrand et al.
6,978,945 B2	12/2005	Wong et al.	8,101,773 B2	1/2012	Smith
7,005,429 B2	2/2006	Dey et al.	8,114,434 B2	2/2012	Sasaki et al.
7,011,846 B2	3/2006	Shojaei et al.	8,158,614 B2	4/2012	Lambert et al.
7,018,992 B2	3/2006	Koch et al.	8,182,833 B2	5/2012	Hermismeyer
7,030,157 B2	4/2006	Ke et al.	8,202,736 B2	6/2012	Mousa et al.
RE39,104 E	5/2006	Duclos et al.	8,217,024 B2	7/2012	Ahmed et al.
7,074,779 B2	7/2006	Sue et al.	8,222,008 B2	7/2012	Thoen
7,083,590 B1	8/2006	Bunt et al.	8,227,454 B2	7/2012	Hill et al.
7,091,213 B2	8/2006	Metcalfe, III et al.	8,227,509 B2	7/2012	Castro et al.
7,101,342 B1	9/2006	Caillouette	8,241,664 B2	8/2012	Dudley et al.
7,135,190 B2	11/2006	Piao et al.	8,247,393 B2	8/2012	Ahmed et al.
7,163,681 B2	1/2007	Giles-Komar et al.	8,273,730 B2	9/2012	Fernandez et al.
7,163,699 B2	1/2007	Besse	8,287,888 B2	10/2012	Song et al.
7,179,799 B2	2/2007	Hill et al.	8,329,680 B2	12/2012	Evans et al.
7,196,074 B2	3/2007	Blye et al.	8,349,820 B2	1/2013	Zeun et al.
7,198,801 B2	4/2007	Carrara et al.	8,420,111 B2	4/2013	Hermismeyer
7,226,910 B2	6/2007	Wilson et al.	8,435,561 B2	5/2013	Besins et al.
7,247,625 B2	7/2007	Zhang et al.	8,658,628 B2	2/2014	Baucom
7,250,446 B2	7/2007	Sangita et al.	8,663,681 B2	3/2014	Ahmed et al.
7,267,829 B2	9/2007	Kirby et al.	2001/0005728 A1	6/2001	Guittard et al.
7,300,926 B2	11/2007	Prokai et al.	2001/0021816 A1	9/2001	Caillouette
7,303,763 B2	12/2007	Ho	2001/0027189 A1	10/2001	Bennink et al.
7,317,037 B2	1/2008	Fensome et al.	2001/0029357 A1	10/2001	Bunt et al.
7,329,654 B2	2/2008	Kanojia et al.	2001/0031747 A1	10/2001	DeZiegler et al.
7,335,650 B2	2/2008	Potter et al.	2001/0034340 A1	10/2001	Pickar
7,374,779 B2	5/2008	Chen et al.	2001/0056068 A1	12/2001	Chwalisz et al.
7,378,404 B2	5/2008	Peters	2002/0012710 A1	1/2002	Lansky
7,387,789 B2	6/2008	Klose et al.	2002/0026158 A1	2/2002	Rathbone et al.
			2002/0028788 A1	3/2002	Bunt et al.
			2002/0058648 A1	5/2002	Hammerly
			2002/0058926 A1	5/2002	Rathbone et al.
			2002/0076441 A1	6/2002	Shih et al.



## US 8,846,648 B2

Page 4

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2002/0102308 A1	8/2002	Wei et al.	2005/0025833 A1	2/2005	Aschkenasy et al.
2002/0107230 A1	8/2002	Waldon et al.	2005/0031651 A1	2/2005	Gervais et al.
2002/0114803 A1	8/2002	Deaver et al.	2005/0042173 A1	2/2005	Besse et al.
2002/0132801 A1	9/2002	Heil et al.	2005/0042268 A1	2/2005	Aschkenasy et al.
2002/0137749 A1	9/2002	Levinson et al.	2005/0048116 A1	3/2005	Straub et al.
2002/0151530 A1	10/2002	Leonard et al.	2005/0079138 A1	4/2005	Chickering, III et al.
2002/0156394 A1	10/2002	Mehrotra et al.	2005/0085453 A1	4/2005	Govindarajan
2002/0169150 A1	11/2002	Pickar	2005/0101579 A1	5/2005	Shippen
2002/0173510 A1	11/2002	Levinson et al.	2005/0113350 A1	5/2005	Duesterberg et al.
2002/0193356 A1	12/2002	Van Beek et al.	2005/0118272 A1	6/2005	Besse et al.
2003/0004145 A1	1/2003	Leonard	2005/0153946 A1	7/2005	Hirsh et al.
2003/0007994 A1	1/2003	Bunt et al.	2005/0164977 A1	7/2005	Coelingh Bennink
2003/0049307 A1	3/2003	Gyurik	2005/0182105 A1	8/2005	Nirschl et al.
2003/0064097 A1	4/2003	Patel et al.	2005/0187267 A1	8/2005	Hamann et al.
2003/0072760 A1	4/2003	Sirbasku	2005/0192253 A1	9/2005	Salvati et al.
2003/0073248 A1	4/2003	Roth et al.	2005/0192310 A1	9/2005	Gavai et al.
2003/0073673 A1	4/2003	Hesch	2005/0207990 A1	9/2005	Funke et al.
2003/0077297 A1	4/2003	Chen et al.	2005/0214384 A1	9/2005	Juturu et al.
2003/0078245 A1	4/2003	Bennink et al.	2005/0220825 A1	10/2005	Funke et al.
2003/0091640 A1	5/2003	Ramanathan et al.	2005/0222106 A1	10/2005	Bracht
2003/0092691 A1	5/2003	Besse et al.	2005/0244522 A1	11/2005	Carrara et al.
2003/0096012 A1	5/2003	Besse et al.	2005/0245902 A1	11/2005	Cornish et al.
2003/0104048 A1	6/2003	Patel et al.	2005/0250746 A1	11/2005	Iammatteo
2003/0114420 A1	6/2003	Salvati et al.	2005/0250750 A1	11/2005	Cummings et al.
2003/0114430 A1	6/2003	MacLeod et al.	2005/0250753 A1	11/2005	Fink et al.
2003/0124182 A1	7/2003	Shojaei et al.	2005/0256028 A1	11/2005	Yun et al.
2003/0124191 A1	7/2003	Besse et al.	2005/0266078 A1	12/2005	Jorda et al.
2003/0130558 A1	7/2003	Massara et al.	2005/0271598 A1	12/2005	Friedman et al.
2003/0144258 A1	7/2003	Heil et al.	2005/0272712 A1	12/2005	Grubb et al.
2003/0157157 A1	8/2003	Luo et al.	2006/0014728 A1	1/2006	Chwalisz et al.
2003/0166509 A1	9/2003	Edwards et al.	2006/0018937 A1	1/2006	Friedman et al.
2003/0180352 A1	9/2003	Patel et al.	2006/0019978 A1	1/2006	Balog
2003/0181353 A1	9/2003	Nyce	2006/0020002 A1	1/2006	Salvati et al.
2003/0181728 A1	9/2003	Salvati et al.	2006/0030615 A1	2/2006	Fensome et al.
2003/0191096 A1	10/2003	Leonard et al.	2006/0034889 A1	2/2006	Jo et al.
2003/0195177 A1	10/2003	Leonard et al.	2006/0051391 A1	3/2006	Dvoskin et al.
2003/0215496 A1	11/2003	Patel et al.	2006/0052341 A1	3/2006	Cornish et al.
2003/0220297 A1	11/2003	Berstein et al.	2006/0069031 A1	3/2006	Loumaye
2003/0224057 A1	12/2003	Martin-Letellier et al.	2006/0083778 A1	4/2006	Allison et al.
2003/0224059 A1	12/2003	Lerner et al.	2006/0089337 A1	4/2006	Casper et al.
2003/0225050 A1	12/2003	Grawe et al.	2006/0093678 A1	5/2006	Chickering, III et al.
2003/0228686 A1	12/2003	Klausner et al.	2006/0106004 A1	5/2006	Brody et al.
2003/0229057 A1	12/2003	Caubel et al.	2006/0110415 A1	5/2006	Gupta
2004/0009960 A1	1/2004	Heil et al.	2006/0111424 A1	5/2006	Salvati et al.
2004/0034001 A1	2/2004	Karara	2006/0121626 A1	6/2006	Imrich
2004/0037881 A1	2/2004	Guittard et al.	2006/0134188 A1	6/2006	Podhaisky et al.
2004/0043943 A1	3/2004	Guittard et al.	2006/0135619 A1	6/2006	Kick et al.
2004/0044080 A1	3/2004	Place et al.	2006/0194775 A1	8/2006	Tofovic et al.
2004/0052824 A1	3/2004	Chacra-Vernet et al.	2006/0204557 A1	9/2006	Gupta et al.
2004/0073024 A1	4/2004	Metcalfe, III et al.	2006/0235037 A1	10/2006	Purandare et al.
2004/0077605 A1	4/2004	Salvati et al.	2006/0240111 A1	10/2006	Fernandez et al.
2004/0077606 A1	4/2004	Salvati et al.	2006/0247216 A1	11/2006	Haj-Yehia
2004/0087548 A1	5/2004	Salvati et al.	2006/0252049 A1	11/2006	Shuler et al.
2004/0089308 A1	5/2004	Welch	2006/0257472 A1	11/2006	Nielsen
2004/0092583 A1	5/2004	Shanahan-Prendergast	2006/0275360 A1	12/2006	Ahmed et al.
2004/0097468 A1	5/2004	Wimalawansa	2006/0280771 A1	12/2006	Groenewegen et al.
2004/0101557 A1	5/2004	Gibson et al.	2006/0280797 A1	12/2006	Shoichet et al.
2004/0106542 A1	6/2004	Deaver et al.	2006/0280800 A1	12/2006	Nagi et al.
2004/0131670 A1	7/2004	Gao	2007/0004693 A1	1/2007	Woolfson et al.
2004/0142012 A1	7/2004	Bunt et al.	2007/0004694 A1	1/2007	Woolfson et al.
2004/0146894 A1	7/2004	Warrington et al.	2007/0021360 A1	1/2007	Nyce et al.
2004/0176324 A1	9/2004	Salvati et al.	2007/0027201 A1	2/2007	McComas et al.
2004/0176336 A1	9/2004	Rodriguez	2007/0031491 A1	2/2007	Levine et al.
2004/0185104 A1	9/2004	Piao et al.	2007/0042038 A1	2/2007	Besse
2004/0191276 A1	9/2004	Muni	2007/0060589 A1	3/2007	Purandare et al.
2004/0198706 A1	10/2004	Carrara	2007/0066628 A1	3/2007	Zhang et al.
2004/0213744 A1	10/2004	Lulla et al.	2007/0066637 A1	3/2007	Zhang et al.
2004/0234606 A1	11/2004	Levine et al.	2007/0066675 A1	3/2007	Zhang et al.
2004/0253319 A1	12/2004	Netke et al.	2007/0088029 A1	4/2007	Balog et al.
2004/0259817 A1	12/2004	Waldon et al.	2007/0093548 A1	4/2007	Diffendal et al.
2004/0266745 A1	12/2004	Schwanitz et al.	2007/0116729 A1	5/2007	Palepu
2005/0004088 A1	1/2005	Hesch	2007/0116829 A1	5/2007	Prakash et al.
2005/0009800 A1	1/2005	Thumbeck et al.	2007/0178166 A1	8/2007	Bernstein et al.
2005/0020552 A1	1/2005	Aschkenasy et al.	2007/0184558 A1	8/2007	Roth et al.
2005/0021009 A1	1/2005	Massara et al.	2007/0191319 A1	8/2007	Ke et al.
			2007/0196433 A1	8/2007	Ron et al.
			2007/0207225 A1	9/2007	Squadraro
			2007/0225281 A1	9/2007	Zhang et al.
			2007/0238713 A1	10/2007	Gast et al.

## US 8,846,648 B2

Page 5

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2007/0243229 A1 10/2007 Smith et al.  
 2007/0264309 A1 11/2007 Chollet et al.  
 2007/0264345 A1 11/2007 Eros et al.  
 2007/0264349 A1 11/2007 Lee et al.  
 2007/0286819 A1 12/2007 DeVries et al.  
 2007/0287789 A1 12/2007 Jones et al.  
 2007/0292387 A1 12/2007 Jon et al.  
 2008/0026035 A1 1/2008 Chollet et al.  
 2008/0026062 A1 1/2008 Farr et al.  
 2008/0038350 A1 2/2008 Gerecke et al.  
 2008/0085877 A1 4/2008 Bortz  
 2008/0095838 A1 4/2008 Abou Chacra-Vernet  
 2008/0113953 A1 5/2008 De Vries et al.  
 2008/0114050 A1 5/2008 Fensome et al.  
 2008/0119537 A1 5/2008 Zhang et al.  
 2008/0125402 A1 5/2008 Diliberti et al.  
 2008/0138379 A1 6/2008 Jennings-Spring  
 2008/0145423 A1 6/2008 Khan et al.  
 2008/0175814 A1 7/2008 Phiasivongsa et al.  
 2008/0188829 A1 8/2008 Creasy  
 2008/0206161 A1 8/2008 Tamarkin et al.  
 2008/0220069 A1 9/2008 Allison  
 2008/0234199 A1 9/2008 Katamreddym  
 2008/0255078 A1 10/2008 Katamreddym  
 2008/0255089 A1 10/2008 Katamreddym  
 2008/0299220 A1 12/2008 Tamarkin et al.  
 2008/0306036 A1 12/2008 Katamreddym  
 2008/0312197 A1 12/2008 Rodriguez  
 2008/0312198 A1 12/2008 Rodriguez  
 2008/0319078 A1 12/2008 Katamreddym  
 2009/0053294 A1 2/2009 Prendergast  
 2009/0060982 A1 3/2009 Ron et al.  
 2009/0068118 A1 3/2009 Eini et al.  
 2009/0081278 A1 3/2009 De Graaff et al.  
 2009/0081303 A1 3/2009 Savoir et al.  
 2009/0092656 A1 4/2009 Klammer et al.  
 2009/0099106 A1 4/2009 Phiasivongsa et al.  
 2009/0131385 A1 5/2009 Voskuhl  
 2009/0137478 A1 5/2009 Bernstein et al.  
 2009/0137538 A1 5/2009 Klammer et al.  
 2009/0143344 A1 6/2009 Chang  
 2009/0181088 A1 7/2009 Song et al.  
 2009/0214474 A1 8/2009 Jennings  
 2009/0227025 A1 9/2009 Nichols et al.  
 2009/0232897 A1 9/2009 Sahoo et al.  
 2009/0258096 A1 10/2009 Cohen  
 2009/0264395 A1 10/2009 Creasy  
 2009/0269403 A1 10/2009 Shaked et al.  
 2009/0285772 A1 11/2009 Phiasivongsa et al.  
 2009/0318558 A1 12/2009 Kim et al.  
 2009/0325916 A1 12/2009 Zhang et al.  
 2010/0028360 A1 2/2010 Atwood  
 2010/0040671 A1 2/2010 Ahmed et al.  
 2010/0048523 A1 2/2010 Bachman et al.  
 2010/0303825 A9 2/2010 Sirbasku  
 2010/0074959 A1 3/2010 Hansom et al.  
 2010/0086599 A1 4/2010 Huempel et al.  
 2010/0092568 A1 4/2010 Lerner et al.  
 2010/0105071 A1 4/2010 Laufer et al.  
 2010/0129320 A1 5/2010 Phiasivongsa et al.  
 2010/0136105 A1 6/2010 Chen et al.  
 2010/0137265 A1 6/2010 Leonard  
 2010/0137271 A1 6/2010 Chen et al.  
 2010/0152144 A1 6/2010 Hermsmeyer  
 2010/0168228 A1 7/2010 Bose et al.  
 2010/0183723 A1 7/2010 Laurent-Applegate  
 2010/0184736 A1 7/2010 Coelingh Bennink et al.  
 2010/0190758 A1 7/2010 Fauser et al.  
 2010/0240626 A1 9/2010 Kulkarni et al.  
 2010/0247632 A1 9/2010 Dong et al.  
 2010/0255085 A1 10/2010 Liu et al.  
 2010/0312137 A1 12/2010 Gilmour et al.  
 2010/0316724 A1 12/2010 Whitfield et al.  
 2010/0330168 A1 12/2010 Gicquel et al.  
 2011/0028439 A1 2/2011 Witt-Enderby et al.

2011/0053845 A1 3/2011 Levine et al.  
 2011/0076775 A1 3/2011 Stewart et al.  
 2011/0076776 A1 3/2011 Stewart et al.  
 2011/0086825 A1 4/2011 Chatroux  
 2011/0091555 A1 4/2011 De Luigi Bruschi et al.  
 2011/0098631 A1 4/2011 McIntyre et al.  
 2011/0104289 A1 5/2011 Savoir Vilboeuf et al.  
 2011/0135719 A1 6/2011 Besins et al.  
 2011/0182997 A1 7/2011 Lewis et al.  
 2011/0195114 A1 8/2011 Carrara et al.  
 2011/0195944 A1 8/2011 Mura et al.  
 2011/0217341 A1 9/2011 Sah  
 2011/0250274 A1 10/2011 Shaked et al.  
 2011/0256092 A1 10/2011 Phiasivongsa et al.  
 2011/0262494 A1 10/2011 Achleitner et al.  
 2011/0268665 A1 11/2011 Tamarkin et al.  
 2011/0293720 A1 12/2011 General et al.  
 2011/0311592 A1 12/2011 Birbara  
 2011/0312927 A1 12/2011 Nachaegari et al.  
 2011/0312928 A1 12/2011 Nachaegari et al.  
 2012/0009276 A1 1/2012 De Groote  
 2012/0015350 A1 1/2012 Nabatiyan et al.  
 2012/0045532 A1 2/2012 Cohen  
 2012/0269878 A2 2/2012 Cantor et al.  
 2012/0052077 A1 3/2012 Truitt et al.  
 2012/0128625 A1 5/2012 Shalwitz et al.  
 2012/0128777 A1 5/2012 Keck et al.  
 2012/0149748 A1 6/2012 Shanler et al.  
 2012/0269721 A1 10/2012 Weng et al.  
 2012/0283671 A1 11/2012 Shibata et al.  
 2013/0022674 A1 1/2013 Dudley et al.  
 2013/0029947 A1 1/2013 Nachaegari et al.  
 2013/0129818 A1 5/2013 Bernick et al.

## FOREIGN PATENT DOCUMENTS

EP 0785212 A1 7/1997  
 EP 1094781 B1 7/2008  
 EP 2191833 A1 6/2010  
 GB 1589946 A1 2/1921  
 GB 452238 A 8/1936  
 GB 720561 A 12/1954  
 GB 848881 A 9/1960  
 GB 874368 A 8/1961  
 IN 216026 A 3/2008  
 IN 2005KO00053 A 9/2009  
 IN 244217 A 11/2010  
 WO 9011064 A1 10/1990  
 WO 9317686 A1 9/1993  
 WO 9422426 A1 10/1994  
 WO 9530409 A1 11/1995  
 WO 9609826 A2 4/1996  
 WO 9630000 A1 10/1996  
 WO 9705491 2/1997  
 WO 9743989 A1 11/1997  
 WO 9810293 A1 3/1998  
 WO 9832465 A1 7/1998  
 WO 9851280 A1 11/1998  
 WO 9932072 A1 7/1999  
 WO 9939700 A1 8/1999  
 WO 9942109 A1 8/1999  
 WO 9943304 9/1999  
 WO 9948477 A1 9/1999  
 WO 9953910 A2 10/1999  
 WO 0038659 A1 11/1999  
 WO 9963974 A2 12/1999  
 WO 0001351 A1 1/2000  
 WO 0006175 A1 2/2000  
 WO 0045795 A2 8/2000  
 WO 0050007 A1 8/2000  
 WO 0059577 A1 10/2000  
 WO 0137808 A1 11/2000  
 WO 0076522 A1 12/2000  
 WO 0154699 A1 8/2001  
 WO 0160325 A1 8/2001  
 WO 0207700 A2 2/2002  
 WO 0211768 A1 2/2002  
 WO 0222132 A2 3/2002  
 WO 0240008 A2 5/2002

## US 8,846,648 B2

Page 6

(56)

## References Cited

## FOREIGN PATENT DOCUMENTS

WO	02053131	A1	7/2002
WO	02078602	A2	10/2002
WO	2002078604	A2	10/2002
WO	03041718	A1	5/2003
WO	03041741	A1	5/2003
WO	03068186	A1	8/2003
WO	03077923	A1	9/2003
WO	03082254	A1	10/2003
WO	03092588	A2	11/2003
WO	2004017983	A1	3/2004
WO	2005027911	A1	3/2004
WO	2004032897	A2	4/2004
WO	2004052336	A2	6/2004
WO	2004054540	A2	7/2004
WO	2004080413	A2	9/2004
WO	2005030175	A1	4/2005
WO	2005087194	A1	9/2005
WO	2005087199	A2	9/2005
WO	2005105059	A1	11/2005
WO	2005115335	A1	12/2005
WO	2005120470	A1	12/2005
WO	2005120517	A1	12/2005
WO	2006013369	A2	2/2006
WO	2006034090	A1	3/2006
WO	2006036899	A2	4/2006
WO	2006053172	A2	5/2006
WO	2006105615	A1	10/2006
WO	2006113505	A2	10/2006
WO	2006138686	A1	12/2006
WO	2006138735	A2	12/2006
WO	2007045027	A1	4/2007
WO	2007103294	A2	9/2007
WO	2007123790	A1	11/2007
WO	2007124250	A2	11/2007
WO	2007144151	A1	12/2007
WO	2008049516	A3	5/2008
WO	2008152444	A2	12/2008
WO	2009002542	A1	12/2008
WO	2009036311	A1	3/2009
WO	2009040818		4/2009
WO	2009069006	A2	6/2009
WO	2009098072	A2	8/2009
WO	2009133352	A2	11/2009
WO	2010033188	A2	3/2010
WO	2011000210	A1	1/2011
WO	2011073995	A2	6/2011
WO	2011120084	A1	10/2011
WO	2011128336	A1	10/2011
WO	2012009778	A2	1/2012
WO	2012024361	A1	2/2012
WO	2013192248	A1	12/2013
WO	2013192249	A1	12/2013
WO	2013192250	A1	12/2013
WO	2013192251	A1	12/2013

## OTHER PUBLICATIONS

International Search Report and Written Opinion for related International Application No. PCT/US12/066406 dated Jan. 24, 2013.  
 International Search Report and Written Opinion for related International Application No. PCT/US13/023309 dated Apr. 9, 2013.  
 International Search Report and Written Opinion for related International Application No. PCT/US13/046442 dated Nov. 1, 2013.  
 International Search Report and Written Opinion for related International Application No. PCT/US13/046443 dated Oct. 31, 2013.  
 International Search Report and Written Opinion for related International Application No. PCT/US13/046444 dated Oct. 31, 2013.  
 International Search Report and Written Opinion for related International Application No. PCT/US13/046445 dated Nov. 1, 2013.  
 USPTO; Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.  
 USPTO; Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002.

USPTO; Notice of Allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002.  
 Acarturk, "Mucoadhesive Vaginal Drug Delivery Systems," Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Exiler-Ankara, Recent Patents on Drug Delivery & Formulation 2009, 3, 193-205.  
 Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," Drug Development and Industrial Pharmacy, 35(5):525-547 (May 2009). Abstract Only.  
 Azure Pharma, Inc., "ELESTRIN™—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages (Aug. 2009).  
 Bhavnani, et al., "Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ERa and ERb", Endocrinology, 149(10): 4857-4870 (Oct. 2008).  
 Bhavnani, et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," J Clin Endocrinol Metab, Mar. 2012, 97(3).  
 Tahition Noni, "Body Balance Cream," [http://products.tni.com/dominican\\_republic/sa\\_spanish/nonistore/product/3438/3416/](http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/), (undated), 1 page.  
 Nugen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, (undated), 3 pages.  
 Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," J. Kor. Pharm. Sci., 35(3):173-177, (2005).  
 Committee of Obstetric Practice, Committee Opinion—No. 522, Obstetrics & Gynecology, 119(4):879-882 (Apr. 2012).  
 Diramio, "Polyethylene Glycol Methacrylate/Dimetacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia-Masters of Science Thesis, 131 pages (2004). [http://atheneum.libs.uga.edu/bitstream/handle/10724/7820/diramio\\_jackie\\_a\\_200412\\_ms.pdf?sequence=1](http://atheneum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1).  
 Du, et al. "Percutaneous Progesterone Delivery Via Cream or Gel Application in Postmenopausal Women: A Randomized Cross-Over Study of Progesterone Levels in Serum, Whole Blood, Saliva, and Capillary Blood," Menopause: The Journal of The North American Menopause Society, vol. 20, No. 11, (Feb. 2013).  
 Fotherby, K., "Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy," Contraception 1996;54:59-69.  
 Fuchs, et al., "The Effects of on Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," Pharmacology / Cosmetology, vol. 5, No. 1, 2006.  
 Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," International Journal of Pharmaceutics, 147(2):165-171 (Feb. 1997). Abstract Only.  
 Hargrove, et al., Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone, vol. 73, No. 4, pp. 606-612 Apr. 1989.  
 Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," Critical Reviews in Toxicology, 30(3):307-345 (2000).  
 Kincl, et al., "Increasing Oral Bioavailability of Progesterone by Formulation," Pergamon Press, Journal of Steroid Biochemistry, 1978, vol. 9, pp. 83-84.  
 Knuth et al., "Hydrogel Delivery Systems for Vaginal and Oral Applications: Formulation and Biological Considerations," Advanced Drug Delivery Reviews, 11(1-2):137-167 (Jul.-Aug. 1993). Abstract Only.  
 Lucy et al., "Gonadotropin-Releasing Hormone at Estrus: Luteinizing Hormone, Estradiol, and Progesterone During the Peri-estrus and Postinsemination Periods in Dairy Cattle," Biol Reprod. 35(2):300-311 (1986). Abstract Only.  
 Position Statement, "Management of Symptomatic Vulvovaginal Atrophy: 2013 Position Statement of the North American Menopause Society," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 9, pp. 888-902, Jun. 2013.  
 NuGest 900™, <http://www.thehormoneshop.net/nugest900.htm>, (undated), 4 pages.

US 8,846,648 B2

Page 7

(56)

## References Cited

## OTHER PUBLICATIONS

- Panay, et al., "The 2013 British Menopause Society & Women's Health Concern Recommendations on Hormone Replacement Therapy," DOI: 0.1177/1754045313489645, *min.sagepub.com*. Menopause International: The Integrated Journal of Postreproductive Health 0(0):1-10, 2013.
- Panchagnula et al., "Development and Evaluation of an Intracutaneous Depot Formulation of Corticosteroids Using Transcutol as a Cosolvent: In-Vitro, Ex-Vivo and In-Vivo Rat Studies," *J Pharm Pharmacol*, 43(9):609-614 (Sep. 1991). Abstract Only.
- Patel, et al., "Transdermal Drug Delivery System: A Review," *www.thepharmajournal.com*, vol. 1 No. 4 2012.
- Salole, "The physicochemical properties of oestradiol," *Journal of Pharmaceutical & Biomedical Analysis*, 5 (7):635-648 (1987).
- Sarrel, et al., "The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years," *American Journal of Public Health*, Published online ahead of print Jul. 18, 2013.
- Shufelt, et al., "Hormone Therapy Dose, Formulation, Route of Delivery, and Risk of Cardiovascular Events in Women: Findings From the Women's Health Initiative Observational Study," *Menopause: The Journal of the North American Menopause Society*, vol. 21, No. 3, 2014.
- Simon, et al., "Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet," *The American College of Obstetricians and Gynecologists*, vol. 112, No. 5, Nov. 2008.
- Sitruk-Ware, et al., "Oral Micronized Progesterone," *Department of Reproductive Endocrinology*, vol. 36, No. 4, pp. 373-402, Oct. 1987.
- Sitruk-Ware, et al., "Progestogens in Hormonal Replacement Therapy: New Molecules, Risks, and Benefits," *Menopause: The Journal of the North American Menopause Society*, vol. 9, No. 1, pp. 6-15, 2002.
- Smith, et al., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens," *JAMA Internal Medicine* <http://archinte.jamanetwork.com>, Sep. 30, 2013.
- Stanczyk, et al. "Ethinyl Estradiol and 17 $\beta$ -Estradiol in Combined Oral Contraceptives: Pharmacokinetics, Pharmacodynamics and Risk Assessment," *Departments of Obstetrics and Gynecology and Preventive Medicine, University of Southern California Keck School of Medicine, Contraception* 87 706-727, (2013).
- Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," *Pharmaceutical Research*, 21(2):201-230 (Feb. 2004).
- Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," *Skin Pharmacol Physiol*, 19:106-121 (2006). [http://www.nanobiotech.igim.unicamp.br/download/Trommer\\_skin%20penetration-2006rev.pdf](http://www.nanobiotech.igim.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf).
- Whitehead, et al., "Absorption and Metabolism of Oral Progesterone," *The British Medical Journal*, vol. 280, No. 6217, Mar. 22, 1980.
- Wood, et al., "Effects of Estradiol with Micronized Progesterone or Medroxyprogesterone Acetate on Risk Markers for Breast Cancer in Postmenopausal Monkeys," *Springer Science+Business Media B.V., Breast Cancer Res Treat* 101:125-134, (2007).
- USPTO; Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545.
- USPTO; Restriction/ Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562.
- USPTO; Restriction/ Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, *Jour. of Mol. Structure, Theochem*, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, *Jour. of Mol. Structure, Theochem* vol. 425, pp. 171-179, 1998, Elsevier.
- Kuhnert-Brandstaetter, M & Kofler, A, Zur Unterscheidung von lösungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II. vol. 1 pp. 127-139, 1968, *Mikrochimica Acta*.
- Kuhnert-Brandstaetter, M & Linder, R, Zur Hydratbildung bei Steroidhormonen, *Sci. Pharm.*, vol. 41(2) pp. 109-116, 1973.
- Kuhnert-Brandstaetter, M, Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , *Drug Development and Industrial Pharmacy*, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-31, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steroids, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G., et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , *Maturitas, The European Menopause Journal*, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroidal conformation of 17 $\alpha$ - and 17 $\beta$ -estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-92, 2012.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17 $\beta$  and Progesterone Concentrations in Uterine Lymph and Systematic Blood . . . , *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, *Catalent Pharma Solutions*, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MONO1500003758.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between  $\alpha$ - and  $\beta$ - Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*, 35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://lxsrv7.ou.edu/~alang/onsc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res*, vol. 31(1), pp. 111-116, 2008.



## US 8,846,648 B2

Page 8

(56)

## References Cited

## OTHER PUBLICATIONS

- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17 $\beta$ -diol solvate: estradiol-methanol-water, *Crystal Structure Comm., Intn'l Union of Crystallography*, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-45, 1999, Elsevier.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gisla L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012%20Patches\_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Salole, Eugene G., Estradiol, *Analytical Profiles of Drug Substances*, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Base . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-26, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, SciFinder, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- SciFinder Scholar Prednisone Chemical Properties, SciFinder, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, SciFinder, 2014, pp. 1-10, Natioinal Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, SciFinder, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Serantoni, Forest!, et al., 4-Pregnen-3,20-dione (progesterone, form II), *Crystal Structure Comm.*, vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Sharma, H. C., et al., Physical Properties of Progesterone Selected Refer, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>, (2014).
- ACOG, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists, ACOG, No. 141, vol. 123, No. 1, Jan. 2014, Obstetrics & Gynecology.
- Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), *Scanning* vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette (2014).
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, *Steroids*, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infared and solution Raman spectroscopic studies of 17 $\beta$ -estradiol and several A-ring . . . , *Vibrational Spectroscopy* 8, Elsevier, pp. 263, 1995.
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, *Bollettino Chimico Farmaceutico*, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>, (2014).
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, *Acta Pharm. Jugosl.*, vol. 40 pp. 71-94, 1990.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, *Am J Obstet Gynecol*, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Molculaire de l'Oestradiol Hemihydrate, *Acta Cryst.*, B28 pp. 560, 1972, Bis(dimethyl-o-thiophenylarsine)palladium(II).
- Busetta, Par Bernard, Structure Cristalline et Molculaire du Complexe Oestradiol-Propanol, *Acta Cryst.*, B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.
- Campsteyn, Par H, et al., Structure Cristalline et Molculaire de la Progesterone C21H30O2, *Acta Cryst.*, B28 pp. 3032-3042, 1972.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, *Revista Mexicana de Fisica*, 50, Suplemento 1 pp. 1-3, 2004.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Commodari, Fernando, Comparison of 17 $\beta$ -estradiol structures from x-ray diffraction and solution NMR, *Magn. Reson. Chem.*, vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, *The Lancet*, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Dideberg, O, et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , *J. Appl. Cryst.* vol. 4 pp. 80, 1971.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , *Inter. Journal of Pharmaceutics*, Elsevier, vol. 363, pp. 40-49, 2009.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, *J. Am. Chem. Soc.*, vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , *J. Thermal Anal.*, vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, SciFinder, *Pharmaceutica Acta Helvetica*, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.

## US 8,846,648 B2

Page 9

(56)

## References Cited

## OTHER PUBLICATIONS

- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.
- Giron, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, *Thermochimica Acta*, vol. 248 pp. 1-59, 1995, Elsevier.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, *J. Pharmaceutical & Biomedical Anal.*, vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, *Acta Cryst.*, vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, *Pharm Res*, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, *Jour. of Mag. Resonance*, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, *Mol. Pharmacology*, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17 $\beta$ -Estradiol Solid Dispersions, *Pharmaceutical Development and Tech.*, vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Idder, Salima, et al., Physicochemical properties of Progesterone, *SciFinder*, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johnson, William S, et al., Racemic Progesterone, *Tetrahedron Letters* No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, *Drug Dev. & Indus. Pharm.*, vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Korkmaz, Filiz, Biophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22 pp. 667-6671, 2000, Elsevier.
- Krzyminiewski, R, et al., EPR Study of the Stable Radical in a  $\gamma$ -radiated Single Crystal of Progesterone, *Jour. of Mag. Resonance*, vol. 46 pp. 300-305, 1982, Academic Press.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Safety Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of *Thevetia peruviana* and *Hura crepitans* Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopoeia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index>[Feb. 3, 2014 1:37:50 PM].
- ChemPro, Top-Notch Technology in Production of Oils and Fats, ChemPro-Edible-Oil-Refining-ISO-TUV-Austria, (2014).
- Corn Refiners Assoc, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Eqbal M. A, et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Ferrari, Roseli AP, et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, Piracicaba, Braz.
- Gunstone, Frank D, et al., Vegetable Oils in Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, *Springerlink.com*, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science*, vol. 47, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Lauroyl Polyoxylglycerides, Safety Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate-Corn Oil, Lot G0L404, Jul. 2013.
- Weber, E.J., Corn Lipids, *Cereal Chem.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Stein, Emily A, et al., Progesterone Physical Properties, *SciFinder*, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone Physical Properties, *SciFinder*, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone, *SciFinder Scholar Search*, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Struhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , *SciFinder, Cesko-Slovenska Farmacie*, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, *Dept of Investigative Med., Univ. Cambridge, Gt. Britain* pp. 531-542, 1972.

**US 8,846,648 B2**

Page 10

(56)

**References Cited****OTHER PUBLICATIONS**

Takacs M, et al., The light sensitivity of corticosteroids in crystalline form, *Pharmaceutica acta Helvetiae*, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.

Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.

Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , *Intl. J. of Pharmaceut.*, vol. 339 pp. 157-167, 2007, Elsevier.

Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, *AAPS PhamSciTech*, vol. 11, No. 3, Sep. 2010.

USP Monographs: Progesterone, USP29, [www.pharmacopeia.cn/v29240/usp29nf24s0\\_m69870.html](http://www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html), search done: Feb. 25, 2014.

Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . *Fertility and Sterility*, vol. 75(6) pp. 1065, Jun. 2001.

Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, *J. SteroidBiochem. Mol. Biol.* (2013), Elsevier.

Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, *Thermochimica Acta* 485, Elsevier, pp. 57, 2009.

Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, *J. of Pharmaceutical Sciences*, vol. 69(8) pp. 912-922, 1980.

Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, *Journal of Steroid Biochem & Mol Biology*, vol. 86 pp. 477-486, 2003.

PCCA, Apothogram, May 2014, pp. 1-14, Houston, TX.

US 6,214,374, 04/2001, Schmirler et al. (withdrawn)

\* cited by examiner

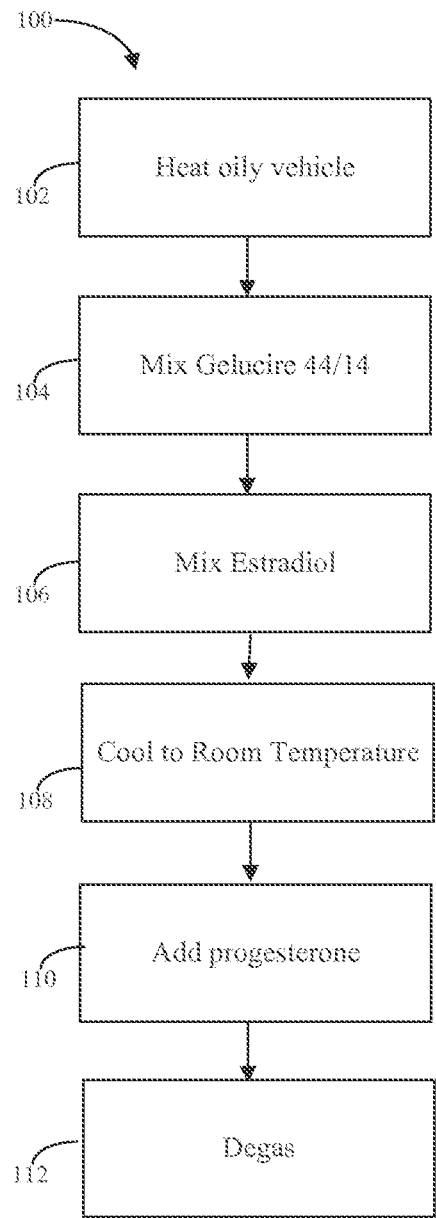
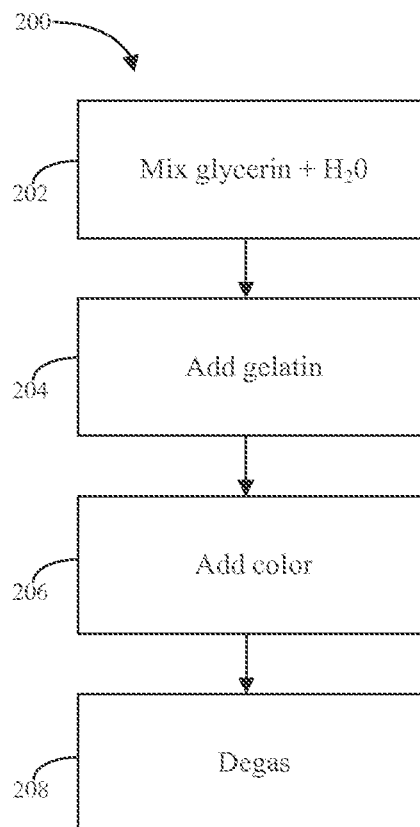


Fig. 1





**Fig. 2**

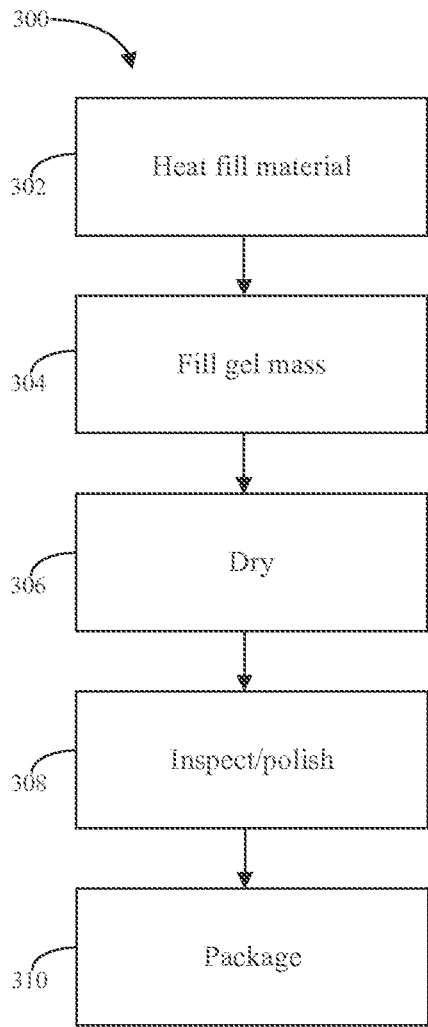


Fig. 3

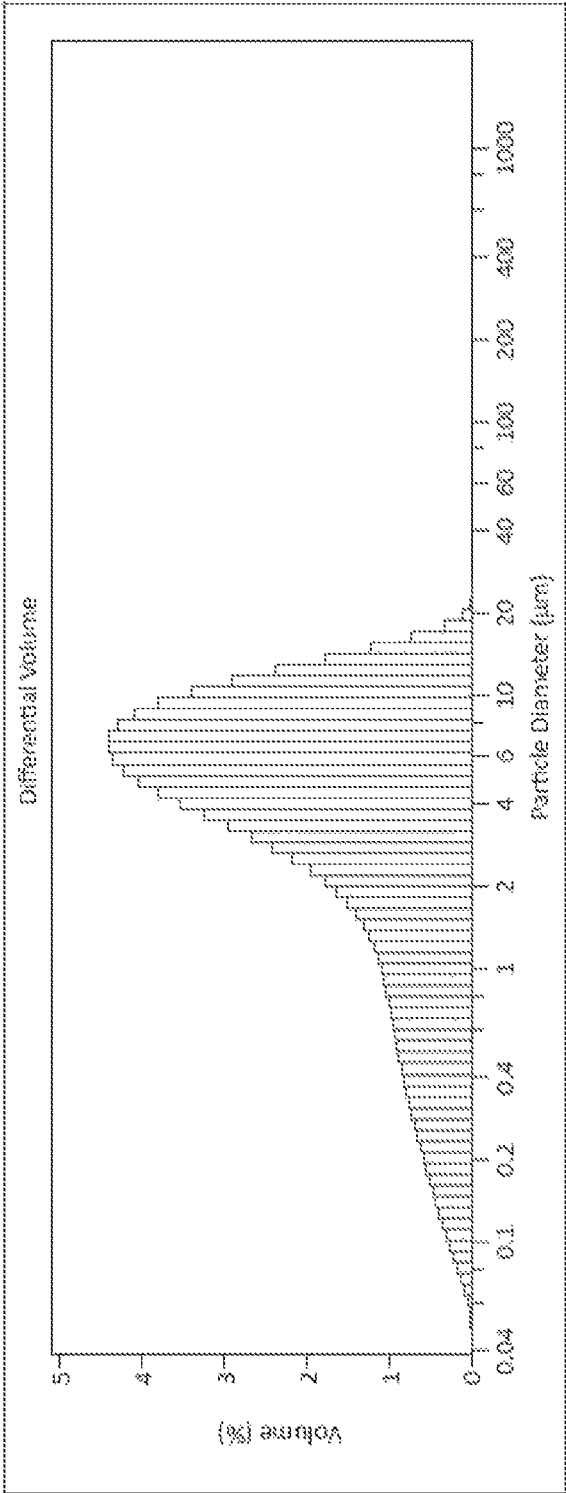


FIG. 4

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## NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

### CROSS REFERENCE TO RELATED APPLICATIONS

This application is a non-provisional application of and claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

### BACKGROUND

#### 1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

#### 2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

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"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as PREM-PRO (conjugated estrogens/medroxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens plus medroxyprogesterone acetate tablets) (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN (conjugated estrogens tablets) (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

### SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

### BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

### DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

#### Definitions

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that

ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to PROMETRIUM (progesterone, USP) at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC,  $C_{max}$ , and optionally,  $T_{max}$ .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ $C_{max}$ ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ $T_{max}$ ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC,  $C_{max}$  and, optionally,  $T_{max}$  are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

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The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

#### Description

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM (progesterone, USP) when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg:50 mg to about 2 mg:1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal

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dosages of PROMETRIUM (progesterone, USP). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM (progesterone, USP) at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM (progesterone, USP) can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 $\beta$ -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary

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dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017  $\mu$ m to 2000  $\mu$ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4  $\mu$ m to 2000  $\mu$ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil;



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generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE (a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride); SASOL Germany GMBH, Hamburg; MIGLYOL (caprylic/capric triglyceride) includes MIGLYOL 810 (Caprylic/Capric Triglyceride), MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 816 (Caprylic/Capric Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL PG-10 (Propylene Glycol Monocaprate); the CAPMUL brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM (Medium Chain Mono- and Diglycerides)); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL (diethylene glycol mono ester)); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL (caprylic/capric triglyceride); TRANSCUTOL (Diethylene glycol monoethyl ether), MIGLYOL (caprylic/capric triglyceride) and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant; and CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for full solubilization of progesterone. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride) can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be

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solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

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As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate,

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medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

## EXAMPLES

### Example 1

#### Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF)	141
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	31.2

\*Literature reference - Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

### Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) at 50%; and also CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL PG-8 (Propylene Glycol Monocaprylate) mixed with MIGLYOL (caprylic/capric triglyceride) at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (85:15)	4.40



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TABLE 2-continued

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	8.60
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	>12
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	>12
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	14.0
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	19.8
Polysorbate 80:CAPMUL MCM (Medium Chain Mono- and Diglycerides) (20:80)	15.0

## Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. MIGLYOL 812 (Caprylic/Capric Triglyceride) with 4% TRANSCUTOL (Diethylene glycol monoethyl ether) precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL (a propylene glycol monocaprylate; propylene glycol monocaprylate) blends at 30 and 50% or in CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride) (4:96)	4	Crystallizes after 96 hours
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	6	Clear, after 14 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	6	Clear, after 14 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	6	Clear after 14 days

12 mg estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate)

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prylate) 50:50, CAPMUL MCM (Medium Chain Mono- and Diglycerides), and in mixtures of TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Clear, after 12 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear after 12 days

## Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization. All CAPMUL PG-8 (Propylene Glycol Monocaprylate) containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL PG-8 (Propylene Glycol Monocaprylate) alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25)	6	Precipitated
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Hazy

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TABLE 5-continued

Formulation	Estradiol mg/g	Results after addition of 7% water
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Hazy
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

## Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF))	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

## Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	322.97	99.38	3.23 kg
Total		100	3.25 kg

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The above formulation is prepared as follows: estradiol is added to CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved.

## Example 7

## Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL (caprylic/capric triglyceride) was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL (caprylic/capric triglyceride) may be used in embodiments comprising a suspension of progesterone, though MIGLYOL (caprylic/capric triglyceride), standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM (Medium Chain Mono- and Diglycerides) is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL (caprylic/capric triglyceride) had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL MCM (Medium Chain Mono- and Diglycerides). It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL MCM (Medium Chain Mono- and Diglycerides).

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	73.4
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	95
MIGLYOL 812 (Caprylic/Capric Triglyceride)	27.8

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM (Medium Chain Mono- and Diglycerides) in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Gelucire 44/14 system, wherein the ratio of CAPMUL MCM (Medium Chain Mono- and Diglycerides) to GELUCIRE 44/14 (Lauroyl macrogol-

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32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (9:1)	86.4
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (7:3)	70.5
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (6:4)	57.4

Example 7

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		82.57	577.97
		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL MCM (Medium Chain Mono- and Diglycerides) may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/- 2° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) may be added to the CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Heat may be removed from the GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) and

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CAPMUL MCM (Medium Chain Mono- and Diglycerides) mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/ Capric Triglyceride) or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/ Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL (caprylic/capric triglyceride) is heated to about 45° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/ diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2%

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w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to about 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL (caprylic/capric triglyceride) may be present in a range from about 35-95% by weight; GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μm, an X75 of 7.442 μm, and an X25 of 1.590 μm. The Beckman Device also yielded that the mean particle size is 4.975 μm, the median particle size is 4.279 μm, the mode particle size is 6.453 μm, and the standard deviation is 3.956 μm. A graph of the particle distribution obtained is shown in FIG. 4.

## Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μm, an X75 of 17.3 μm, and an X25 of 5.3 μm. The Beckman Device also yielded that the mean particle size is 11.8 μm, the median particle size is 11.04 μm, the mode particle size is 13.6 μm, and the standard deviation is 7.8 μm.

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## Example 12

In order to increase the solubility of progesterone in the final solution, GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
15	1. Progesterone, USP, micronized	50.00	7.14	50.00	0.50
	2. Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
	3. CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97	5.78
20	4. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG))		10.0	70.00	0.70
25	Gelucire 44/14, NF				
30	Total:	100.00	700.00	7.00	

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 40° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

## Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
50	1. Progesterone, USP, micronized	50.00	25.000	50.00	500.00
	2. Estradiol Hemihydrate	0.25	0.129	0.26	2.58
	3. CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		73.371	146.74	1467.42
55	4. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.500	3.00	30.00
60	Total:	100.000	200.00 mg	2000.00	

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C.

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GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33 200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35 2.07	20.7
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		65.32 391.93	3919.3
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.00 6.0	60.0
Total:		100.00	600.0 mg	6000.0

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 15

Progesterone and Estradiol Combination Study under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM (progesterone, USP) (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

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Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM (progesterone, USP) soft gel Capsule 200 mg and ESTRACE (estradiol vaginal cream, USP, 0.01%) (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ±20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration



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of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

## Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+/-3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled

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volumes. Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/-10° C. The wedge temperature may be 38° C.+/-3° C. The drum cooling temperature may be 4° C.+/-2° C. The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/-10° C. The wedge temperature may be 38° C.+/-3° C. The drum cooling temperature may be 4° C.+/-2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A method of treating a menopause-related symptom in a woman comprising:

administering to the woman an effective amount of a pharmaceutical composition, the pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed;

wherein the solubilizing agent contains an effective amount of C6-C12 oil; and

wherein at least about 90% of the estradiol is solubilized in the solubilizing agent.

2. The method of claim 1, further comprising partially solubilized progesterone, the partially solubilized progesterone being solubilized in the solubilizing agent.

3. The method of claim 1, wherein the composition is formulated as a gelatin capsule.

4. The method of claim 1, wherein the C6-C12 oil is selected from at least one of mono-, di-, and triglycerides and combinations thereof.

5. The method of claim 1, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

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6. The method of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

7. The method of claim 1, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and to a 2 mg estradiol tablet.

8. A method of treating a menopause symptom in a woman comprising administering a pharmaceutical composition to the woman, the pharmaceutical composition comprising:

solubilized estradiol;

suspended progesterone; and

a solubilizing agent, the solubilizing agent containing an effective amount of a C6-C12 oil;

wherein the estradiol and the suspended progesterone are present in the solubilizing agent, the estradiol and the suspended progesterone are uniformly dispersed and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the estradiol does not precipitate for at least 14 days.

9. The method of claim 8, further comprising partially solubilized progesterone, the partially solubilized progesterone being solubilized in the solubilizing agent.

10. The method of claim 8, wherein the composition is formulated as a gelatin capsule.

11. The method of claim 8, wherein the C6-C12 oil is selected from at least one of mono-, di-, and triglycerides and combinations thereof.

12. The method of claim 8, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

13. The method of claim 8, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

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14. The method of claim 8, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and to a 2 mg estradiol tablet.

15. A method of treating a menopause symptom comprising:

administering an effective amount of a pharmaceutical composition to a woman, the pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent, the estradiol being stable in the solubilizing agent for at least 14 days; wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed;

wherein at least about 90% of the estradiol is solubilized in the solubilizing agent, and wherein the solubilizing agent contains an effective amount of a C6-C12 oil.

16. The method of claim 15, further comprising partially solubilized progesterone, the partially solubilized progesterone being solubilized in the solubilizing agent.

17. The method of claim 15, wherein the composition is formulated as a gelatin capsule.

18. The method of claim 15, wherein the C6-C12 oil is selected from at least one of mono-, di-, and triglycerides and combinations thereof.

19. The method of claim 15, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

20. The method of claim 15, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,846,648 B2  
APPLICATION NO. : 14/099545  
DATED : September 30, 2014  
INVENTOR(S) : Brian A. Bernick et al.

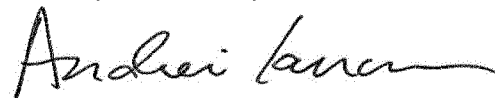
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this  
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu  
*Director of the United States Patent and Trademark Office*



UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,846,648 B2  
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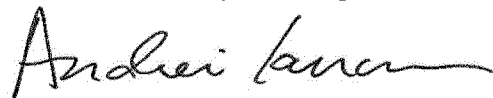
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 24, Claim 15, Line 16: Delete “agnt” and insert in its place --agent--.

Signed and Sealed this  
Twentieth Day of August, 2019



Andrei Iancu  
*Director of the United States Patent and Trademark Office*

# EXHIBIT C



US008846649B2

(12) **United States Patent**  
**Bernick et al.**

(10) **Patent No.:** **US 8,846,649 B2**  
(45) **Date of Patent:** **\*Sep. 30, 2014**

(54) **NATURAL COMBINATION HORMONE  
REPLACEMENT FORMULATIONS AND  
THERAPIES**

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(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.  
  
This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/099,571**

(22) Filed: **Dec. 6, 2013**

(65) **Prior Publication Data**

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(51) **Int. Cl.**

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**A61K 9/48** (2006.01)

**A61K 9/16** (2006.01)

**A61K 31/57** (2006.01)

**A61K 31/565** (2006.01)

(52) **U.S. Cl.**

CPC ..... **A61K 31/57** (2013.01); **A61K 9/4858** (2013.01); **A61K 9/16** (2013.01); **A61K 31/565** (2013.01)

USPC ..... **514/169**; **424/452**

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

1,967,351 A 7/1934 Doisy  
2,379,832 A 7/1945 Serini et al.  
2,649,399 A 8/1953 Grant et al.  
3,198,707 A 8/1965 Nomaine et al.  
3,478,070 A 11/1969 Smith et al.  
3,526,648 A 9/1970 Bertin et al.

3,710,795 A 1/1973 Higuchi et al.  
3,729,560 A 4/1973 Hagerman  
3,729,566 A 4/1973 Ericsson et al.  
3,755,573 A 8/1973 Berman  
3,755,575 A 8/1973 Lerner  
3,903,880 A 9/1975 Higuchi et al.  
3,916,898 A 11/1975 Robinson  
3,916,899 A 11/1975 Higuchi et al.  
3,921,636 A 11/1975 Zaffaroni  
3,923,997 A 12/1975 Meuly  
3,948,254 A 4/1976 Zaffaroni  
3,971,367 A 7/1976 Zaffaroni  
3,977,404 A 8/1976 Theeuwes  
3,993,072 A 11/1976 Zaffaroni  
4,008,719 A 2/1977 Theeuwes  
4,012,496 A 3/1977 Hartmann  
4,014,334 A 3/1977 Theeuwes et al.  
4,014,987 A 3/1977 Heller et al.  
4,016,251 A 4/1977 Higuchi et al.  
4,071,623 A 1/1978 van Der Vies  
4,093,709 A 6/1978 Choi  
4,154,820 A 5/1979 Simoons  
4,155,991 A 5/1979 Schopflin et al.  
4,196,188 A 4/1980 Besins  
4,215,691 A 8/1980 Wong  
4,237,885 A 12/1980 Wong  
4,310,510 A 1/1982 Sherman et al.  
4,327,725 A 5/1982 Cortese et al.  
4,372,951 A 2/1983 Vorys  
4,384,096 A 5/1983 Sonnabend  
4,393,871 A 7/1983 Vorhauer  
4,402,695 A 9/1983 Wong  
4,423,151 A 12/1983 Baranczuk  
4,449,980 A 5/1984 Millar et al.  
4,610,687 A 9/1986 Fogwell  
4,629,449 A 12/1986 Wong

(Continued)

**FOREIGN PATENT DOCUMENTS**

BR PI 1001367-9 A2 7/2012  
CN 102258455 A 11/2011

(Continued)

**OTHER PUBLICATIONS**

US 6,214,374, 4/2001, Schmirler, et al. (withdrawn).  
International Search Report and Written Opinion for related International Application No. PCT/US12/066406 dated Jan. 24, 2013.  
International Search Report and Written Opinion for related International Application No. PCT/US13/023309 dated Apr. 9, 2013.

(Continued)

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(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

**15 Claims, 4 Drawing Sheets**

## US 8,846,649 B2

Page 2

(56)

## References Cited

## U.S. PATENT DOCUMENTS

4,732,763	A	3/1988	Beck et al.	5,922,349	A	7/1999	Elliesen et al.
4,738,957	A	4/1988	Laurent et al.	5,928,666	A	7/1999	Farinas et al.
4,756,907	A	7/1988	Beck et al.	5,958,446	A	9/1999	Miranda et al.
4,762,717	A	8/1988	Crowley	5,962,445	A	10/1999	Stewart
4,788,062	A	11/1988	Gale et al.	5,972,372	A	10/1999	Saleh et al.
4,816,257	A	3/1989	Buster et al.	5,985,861	A	11/1999	Levine et al.
4,822,616	A	4/1989	Zimmermann et al.	5,993,856	A	11/1999	Ragavan et al.
4,865,848	A	9/1989	Cheng et al.	6,001,846	A	12/1999	Edwards et al.
4,900,734	A	2/1990	Maxson et al.	6,022,562	A	2/2000	Autant et al.
4,906,475	A	3/1990	Kim	6,024,976	A	2/2000	Miranda et al.
4,942,158	A	7/1990	Sarpotdar et al.	6,028,057	A	2/2000	Burns
4,961,931	A	10/1990	Wong	6,039,968	A	3/2000	Nabahi
5,030,629	A	7/1991	Rajadhyaksha	6,056,972	A	5/2000	Hermesmyer
5,064,654	A	11/1991	Berner et al.	6,060,077	A	5/2000	Meignant
5,108,995	A	4/1992	Casper	6,074,625	A	6/2000	Hawthorne et al.
5,128,138	A	7/1992	Blank	6,077,531	A	6/2000	Salin-Drouin
5,130,137	A	7/1992	Crowley	6,080,118	A	6/2000	Blythe
5,140,021	A	8/1992	Maxson et al.	6,083,178	A	7/2000	Caillouette
5,211,952	A	5/1993	Pike et al.	6,086,916	A	7/2000	Agnus et al.
5,252,334	A	10/1993	Chiang et al.	6,096,338	A	8/2000	Lacy et al.
5,280,023	A	1/1994	Ehrlich et al.	6,117,446	A	9/2000	Place
5,288,496	A	2/1994	Lewis	6,117,450	A	9/2000	Dittgen et al.
5,340,584	A	8/1994	Spicer et al.	6,133,251	A	10/2000	Dittgen et al.
5,340,585	A	8/1994	Pike et al.	6,133,320	A	10/2000	Yallampalli et al.
5,340,586	A	8/1994	Pike et al.	6,139,873	A	10/2000	Hughes, Jr. et al.
5,362,497	A	11/1994	Yamada et al.	6,153,216	A	11/2000	Cordes et al.
5,382,573	A	1/1995	Casper	6,165,491	A	12/2000	Grasset et al.
5,393,528	A	2/1995	Staab	6,165,975	A	12/2000	Adams et al.
5,393,529	A	2/1995	Hoffmann et al.	6,187,339	B1	2/2001	de Haan et al.
5,419,910	A	5/1995	Lewis	6,190,331	B1	2/2001	Caillouette
5,468,736	A	11/1995	Hodgen	6,201,072	B1	3/2001	Rathi et al.
5,474,783	A	12/1995	Miranda et al.	6,227,202	B1	5/2001	Matapurkar
5,480,776	A	1/1996	Dullien	6,262,115	B1	7/2001	Guittard et al.
5,514,673	A	5/1996	Heckenmuller et al.	6,277,418	B1	8/2001	Markaverich et al.
5,516,528	A	5/1996	Hughes et al.	6,283,927	B1	9/2001	Caillouette
5,527,534	A	6/1996	Myhling	6,287,588	B1	9/2001	Shih et al.
5,529,782	A	6/1996	Staab	6,287,693	B1	9/2001	Savoir et al.
5,543,150	A	8/1996	Bologna et al.	6,294,188	B1	9/2001	Ragavan et al.
5,547,948	A	8/1996	Barcomb	6,294,192	B1	9/2001	Patel et al.
5,565,199	A	10/1996	Page et al.	6,294,550	B1	9/2001	Place et al.
5,567,831	A	10/1996	Li	6,299,900	B1	10/2001	Reed et al.
5,569,652	A	10/1996	Beier et al.	6,306,841	B1	10/2001	Place et al.
5,582,592	A	12/1996	Kendrick	6,306,914	B1	10/2001	de Ziegler et al.
5,585,370	A	12/1996	Casper	6,309,669	B1	10/2001	Setterstrom et al.
5,595,759	A	1/1997	Wright et al.	6,309,848	B1	10/2001	Howett et al.
5,595,970	A	1/1997	Garfield et al.	6,342,491	B1	1/2002	Dey et al.
5,620,705	A	4/1997	Dong et al.	6,372,209	B1	4/2002	Chrisope
5,629,021	A	5/1997	Wright	6,372,246	B1	4/2002	Wei
5,633,011	A	5/1997	Dong et al.	6,387,390	B1	5/2002	Deaver et al.
5,633,242	A	5/1997	Ottel et al.	6,402,705	B1	6/2002	Caillouette
5,639,743	A	6/1997	Kaswan et al.	6,416,778	B1	7/2002	Ragavan et al.
5,656,286	A	8/1997	Miranda et al.	6,423,039	B1	7/2002	Rathbone et al.
5,676,968	A	10/1997	Lipp et al.	6,423,683	B1	7/2002	Heaton et al.
5,677,292	A	10/1997	Li et al.	6,436,633	B1	8/2002	Kreider et al.
5,694,947	A	12/1997	Lehtinen et al.	6,440,454	B1	8/2002	Santoro et al.
5,709,844	A	1/1998	Arbeit et al.	6,444,224	B1	9/2002	Rathbone et al.
5,735,801	A	4/1998	Caillouette	6,444,234	B1	9/2002	Kirby et al.
5,739,176	A	4/1998	Dunn et al.	6,451,339	B2	9/2002	Patel et al.
5,744,463	A	4/1998	Bair	6,451,779	B1	9/2002	Hesch
5,747,058	A	5/1998	Tipton et al.	6,455,246	B1	9/2002	Howell et al.
5,762,614	A	6/1998	Caillouette	6,455,517	B1	9/2002	Tanabe et al.
5,770,176	A	6/1998	Nargessi	6,468,526	B2	10/2002	Chrisope
5,770,219	A	6/1998	Chiang et al.	6,469,016	B1	10/2002	Place et al.
5,776,495	A	7/1998	Duclos et al.	6,472,434	B1	10/2002	Place et al.
5,788,980	A	8/1998	Nabahi	6,479,232	B1	11/2002	Howett et al.
5,789,442	A	8/1998	Garfield et al.	6,500,814	B1	12/2002	Hesch
5,811,416	A	9/1998	Chwalisz	6,503,896	B1	1/2003	Tanabe et al.
5,811,547	A	9/1998	Nakamichi et al.	6,511,969	B1	1/2003	Hermesmyer
5,814,329	A	9/1998	Shah	6,526,980	B1	3/2003	Tracy et al.
5,827,200	A	10/1998	Caillouette	6,528,094	B1	3/2003	Savoir et al.
5,866,603	A	2/1999	Li et al.	6,537,580	B1	3/2003	Savoir et al.
5,891,868	A	4/1999	Cummings et al.	6,544,196	B2	4/2003	Caillouette
5,898,038	A	4/1999	Yallampalli et al.	6,544,553	B1	4/2003	Hsia et al.
5,916,176	A	6/1999	Caillouette	6,548,491	B2	4/2003	Tanabe et al.
RE36,247	E	7/1999	Plunkett et al.	6,551,611	B2	4/2003	Elliesen et al.
				6,569,463	B2	5/2003	Patel et al.
				6,583,129	B1	6/2003	Mazer et al.
				6,586,006	B2	7/2003	Roser et al.
				6,589,549	B2	7/2003	Shih et al.

## US 8,846,649 B2

Page 3

(56)

## References Cited

## U.S. PATENT DOCUMENTS

6,593,317 B1	7/2003	De Ziegler et al.	7,465,587 B2	12/2008	Imrich
6,610,670 B2	8/2003	Backensfeld et al.	7,470,433 B2	12/2008	Carrara et al.
6,638,536 B2	10/2003	Savoir et al.	7,485,666 B2	2/2009	Villanueva et al.
6,645,528 B1	11/2003	Straub et al.	7,497,855 B2	3/2009	Ausiello et al.
6,653,298 B2	11/2003	Potter et al.	7,534,765 B2	5/2009	Gregg et al.
6,656,929 B1	12/2003	Agnus et al.	7,550,142 B2	6/2009	Giles-Komar et al.
6,660,726 B2	12/2003	Hill et al.	7,563,565 B1	7/2009	Matsuo et al.
6,663,608 B2	12/2003	Rathbone et al.	7,572,779 B2	8/2009	Aloba et al.
6,663,895 B2	12/2003	Savoir et al.	7,572,780 B2	8/2009	Hermismeyer
6,692,763 B1	2/2004	Cummings et al.	7,589,082 B2	9/2009	Savoir et al.
6,737,081 B2	5/2004	Savoir et al.	7,671,027 B2	3/2010	Loumaye
6,740,333 B2	5/2004	Beckett et al.	7,674,783 B2	3/2010	Hermismeyer
6,743,815 B2	6/2004	Huebner et al.	7,687,281 B2	3/2010	Roth et al.
6,747,018 B2	6/2004	Tanabe et al.	7,687,485 B2	3/2010	Levinson et al.
6,756,208 B2	6/2004	Griffin et al.	7,694,683 B2	4/2010	Callister et al.
6,776,164 B2	8/2004	Bunt et al.	7,704,983 B1	4/2010	Hodgen et al.
6,787,152 B2	9/2004	Kirby et al.	7,727,720 B2	6/2010	Dhallan
6,805,877 B2	10/2004	Massara et al.	7,732,408 B2	6/2010	Josephson et al.
6,809,085 B1	10/2004	Elson et al.	7,749,989 B2	7/2010	Hill et al.
6,818,226 B2	11/2004	Reed et al.	7,767,656 B2	8/2010	Shoichet et al.
6,841,716 B1	1/2005	Tsutsumi	7,815,949 B2	10/2010	Cohen
6,844,334 B2	1/2005	Hill et al.	7,829,115 B2	11/2010	Besins et al.
6,855,703 B1	2/2005	Hill et al.	RE42,012 E	12/2010	Deaver et al.
6,860,859 B2	3/2005	Mehrotra et al.	7,858,607 B2	12/2010	Mamchur
6,866,865 B2	3/2005	Hsia et al.	RE42,072 E	1/2011	Deaver et al.
6,869,969 B2	3/2005	Huebner et al.	7,862,552 B2	1/2011	McIntyre et al.
6,878,518 B2	4/2005	Whitehead	7,867,990 B2	1/2011	Schultz et al.
6,901,278 B1	5/2005	Notelovitz	7,879,830 B2	2/2011	Wiley
6,905,705 B2	6/2005	Palm et al.	7,884,093 B2	2/2011	Creasy et al.
6,911,438 B2	6/2005	Wright	7,939,104 B2	5/2011	Barbera et al.
6,923,988 B2	8/2005	Patel et al.	7,943,602 B2	5/2011	Bunschoten et al.
6,924,274 B2	8/2005	Lardy et al.	7,943,604 B2	5/2011	Coelingh Bennik et al.
6,932,983 B1	8/2005	Straub et al.	7,989,436 B2	8/2011	Hill et al.
6,939,558 B2	9/2005	Massara et al.	7,989,487 B2	8/2011	Welsh et al.
6,943,021 B2	9/2005	Klausner et al.	8,022,053 B2	9/2011	Mueller et al.
6,958,327 B1	10/2005	Hillisch et al.	8,048,869 B2	11/2011	Bunschoten et al.
6,962,691 B1	11/2005	Lulla et al.	8,071,729 B2	12/2011	Giles-Komar et al.
6,962,908 B2	11/2005	Aloba et al.	8,076,319 B2	12/2011	Leonard
6,967,194 B1	11/2005	Matsuo et al.	8,088,605 B2	1/2012	Beaudet et al.
6,977,250 B2	12/2005	Rodriguez	8,101,209 B2	1/2012	LeGrand et al.
6,978,945 B2	12/2005	Wong et al.	8,101,773 B2	1/2012	Smith
7,005,429 B2	2/2006	Dey et al.	8,114,434 B2	2/2012	Sasaki et al.
7,011,846 B2	3/2006	Shojaei et al.	8,158,614 B2	4/2012	Lambert et al.
7,018,992 B2	3/2006	Koch et al.	8,182,833 B2	5/2012	Hermismeyer
7,030,157 B2	4/2006	Ke et al.	8,202,736 B2	6/2012	Mousa et al.
RE39,104 E	5/2006	Duclos et al.	8,217,024 B2	7/2012	Ahmed et al.
7,074,779 B2	7/2006	Sue et al.	8,222,008 B2	7/2012	Thone
7,083,590 B1	8/2006	Bunt et al.	8,227,454 B2	7/2012	Hill et al.
7,091,213 B2	8/2006	Metcalfe, III et al.	8,227,509 B2	7/2012	Castro et al.
7,101,342 B1	9/2006	Caillouette	8,241,664 B2	8/2012	Dudley et al.
7,135,190 B2	11/2006	Piao et al.	8,247,393 B2	8/2012	Ahmed et al.
7,163,681 B2	1/2007	Giles-Komar	8,273,730 B2	9/2012	Fernandez et al.
7,163,699 B2	1/2007	Besse	8,287,888 B2	10/2012	Song et al.
7,179,799 B2	2/2007	Hill et al.	8,329,680 B2	12/2012	Evans et al.
7,196,074 B2	3/2007	Blye et al.	8,349,820 B2	1/2013	Zeun et al.
7,198,801 B2	4/2007	Carrara et al.	8,420,111 B2	4/2013	Hermismeyer
7,226,910 B2	6/2007	Wilson et al.	8,435,561 B2	5/2013	Besins et al.
7,247,625 B2	7/2007	Zhang et al.	8,658,628 B2	2/2014	Baucom
7,250,446 B2	7/2007	Sangita et al.	8,663,681 B2	3/2014	Ahmed et al.
7,267,829 B2	9/2007	Kirby et al.	2001/0005728 A1	6/2001	Guittard et al.
7,300,926 B2	11/2007	Prokai et al.	2001/0021816 A1	9/2001	Caillouette
7,303,763 B2	12/2007	Ho	2001/0027189 A1	10/2001	Bennink et al.
7,317,037 B2	1/2008	Fensome et al.	2001/0029357 A1	10/2001	Bunt et al.
7,329,654 B2	2/2008	Kanojia et al.	2001/0031747 A1	10/2001	DeZiegler et al.
7,335,650 B2	2/2008	Potter et al.	2001/0034340 A1	10/2001	Pickar
7,374,779 B2	5/2008	Chen et al.	2001/0056068 A1	12/2001	Chwalisz et al.
7,378,404 B2	5/2008	Peters	2002/0012710 A1	1/2002	Lansky
7,387,789 B2	6/2008	Klose et al.	2002/0026158 A1	2/2002	Rathbone et al.
7,388,006 B2	6/2008	Schmees et al.	2002/0028788 A1	3/2002	Bunt et al.
7,414,043 B2	8/2008	Kosemund et al.	2002/0058648 A1	5/2002	Hammerly
7,427,413 B2	9/2008	Savoir et al.	2002/0058926 A1	5/2002	Rathbone et al.
7,427,609 B2	9/2008	Leonard	2002/0076441 A1	6/2002	Shih et al.
7,429,576 B2	9/2008	Labrie	2002/0102308 A1	8/2002	Wei et al.
7,431,941 B2	10/2008	Besins et al.	2002/0107230 A1	8/2002	Waldon et al.
7,459,445 B2	12/2008	Hill et al.	2002/0114803 A1	8/2002	Deaver et al.
			2002/0132801 A1	9/2002	Heil et al.
			2002/0137749 A1	9/2002	Levinson et al.
			2002/0151530 A1	10/2002	Leonard et al.
			2002/0156394 A1	10/2002	Mehrotra et al.

## US 8,846,649 B2

Page 4

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2002/0169150	A1	11/2002	Pickar	2005/0101579	A1	5/2005	Shippen
2002/0173510	A1	11/2002	Levinson et al.	2005/0113350	A1	5/2005	Duesterberg et al.
2002/0193356	A1	12/2002	Van Beek et al.	2005/0118272	A1	6/2005	Besse et al.
2003/0004145	A1	1/2003	Leonard	2005/0153946	A1	7/2005	Hirsh et al.
2003/0007994	A1	1/2003	Bunt et al.	2005/0164977	A1	7/2005	Coelingh Bennink
2003/0049307	A1	3/2003	Gyurik	2005/0182105	A1	8/2005	Nirschl et al.
2003/0064097	A1	4/2003	Patel et al.	2005/0187267	A1	8/2005	Hamann et al.
2003/0072760	A1	4/2003	Sirbasku	2005/0192253	A1	9/2005	Salvati et al.
2003/0073248	A1	4/2003	Roth et al.	2005/0192310	A1	9/2005	Gavai et al.
2003/0073673	A1	4/2003	Hesch	2005/0207990	A1	9/2005	Funke et al.
2003/0077297	A1	4/2003	Chen et al.	2005/0214384	A1	9/2005	Juturu et al.
2003/0078245	A1	4/2003	Bennink et al.	2005/0220825	A1	10/2005	Funke et al.
2003/0091640	A1	5/2003	Ramanathan et al.	2005/0222106	A1	10/2005	Bracht
2003/0092691	A1	5/2003	Besse et al.	2005/0244522	A1	11/2005	Carrara et al.
2003/0096012	A1	5/2003	Besse et al.	2005/0245902	A1	11/2005	Cornish et al.
2003/0104048	A1	6/2003	Patel et al.	2005/0250746	A1	11/2005	Iammatteo
2003/0114420	A1	6/2003	Salvati et al.	2005/0250750	A1	11/2005	Cummings et al.
2003/0114430	A1	6/2003	MacLeod et al.	2005/0250753	A1	11/2005	Fink et al.
2003/0124182	A1	7/2003	Shojaci et al.	2005/0256028	A1	11/2005	Yun et al.
2003/0124191	A1	7/2003	Besse et al.	2005/0266078	A1	12/2005	Jorda et al.
2003/0130558	A1	7/2003	Massara et al.	2005/0271598	A1	12/2005	Frieman et al.
2003/0144258	A1	7/2003	Heil et al.	2005/0272712	A1	12/2005	Grubb et al.
2003/0157157	A1	8/2003	Luo et al.	2006/0014728	A1	1/2006	Chwalisz et al.
2003/0166509	A1	9/2003	Edwards et al.	2006/0018937	A1	1/2006	Friedman et al.
2003/0180352	A1	9/2003	Patel et al.	2006/0019978	A1	1/2006	Balog
2003/0181353	A1	9/2003	Nyce	2006/0020002	A1	1/2006	Salvati et al.
2003/0181728	A1	9/2003	Salvati et al.	2006/0030615	A1	2/2006	Fensome et al.
2003/0191096	A1	10/2003	Leonard et al.	2006/0034889	A1	2/2006	Jo et al.
2003/0195177	A1	10/2003	Leonard et al.	2006/0051391	A1	3/2006	Dvoskin et al.
2003/0215496	A1	11/2003	Patel et al.	2006/0052341	A1	3/2006	Cornish et al.
2003/0220297	A1	11/2003	Berstein et al.	2006/0069031	A1	3/2006	Loumaye
2003/0224057	A1	12/2003	Martin-Letellier et al.	2006/0083778	A1	4/2006	Allison et al.
2003/0224059	A1	12/2003	Lerner et al.	2006/0089337	A1	4/2006	Casper et al.
2003/0225050	A1	12/2003	Grawe et al.	2006/0093678	A1	5/2006	Chickering, III et al.
2003/0228686	A1	12/2003	Klausner et al.	2006/0106004	A1	5/2006	Brody et al.
2003/0229057	A1	12/2003	Caubel et al.	2006/0110415	A1	5/2006	Gupta
2004/0009960	A1	1/2004	Heil et al.	2006/0111424	A1	5/2006	Salvati et al.
2004/0034001	A1	2/2004	Karara	2006/0121626	A1	6/2006	Imrich
2004/0037881	A1	2/2004	Guittard et al.	2006/0134188	A1	6/2006	Podhaisky et al.
2004/0043943	A1	3/2004	Guittard et al.	2006/0135619	A1	6/2006	Kick et al.
2004/0044080	A1	3/2004	Place et al.	2006/0194775	A1	8/2006	Tofovic et al.
2004/0052824	A1	3/2004	Chacra-Vernet et al.	2006/0204557	A1	9/2006	Gupta et al.
2004/0073024	A1	4/2004	Metcalfe, III et al.	2006/0235037	A1	10/2006	Purandare et al.
2004/0077605	A1	4/2004	Salvati et al.	2006/0240111	A1	10/2006	Fernandez et al.
2004/0077606	A1	4/2004	Salvati et al.	2006/0247216	A1	11/2006	Haj-Yehia
2004/0087548	A1	5/2004	Salvati et al.	2006/0252049	A1	11/2006	Shuler et al.
2004/0089308	A1	5/2004	Welch	2006/0257472	A1	11/2006	Neilsen
2004/0092583	A1	5/2004	Shanahan-Prendergast	2006/0275360	A1	12/2006	Ahmed et al.
2004/0097468	A1	5/2004	Wimalawansa	2006/0280771	A1	12/2006	Groenewegen et al.
2004/0101557	A1	5/2004	Gibson et al.	2006/0280797	A1	12/2006	Shoichet et al.
2004/0106542	A1	6/2004	Deaver et al.	2006/0280800	A1	12/2006	Nagi et al.
2004/0131670	A1	7/2004	Gao	2007/0004693	A1	1/2007	Woolfson et al.
2004/0142012	A1	7/2004	Bunt et al.	2007/0004694	A1	1/2007	Woolfson et al.
2004/0146894	A1	7/2004	Warrington et al.	2007/0021360	A1	1/2007	Nyce et al.
2004/0176324	A1	9/2004	Salvati et al.	2007/0027201	A1	2/2007	McComas et al.
2004/0176336	A1	9/2004	Rodriguez	2007/0031491	A1	2/2007	Levine et al.
2004/0185104	A1	9/2004	Piao et al.	2007/0042038	A1	2/2007	Besse
2004/0191276	A1	9/2004	Muni	2007/0060589	A1	3/2007	Purandare et al.
2004/0198706	A1	10/2004	Carrara	2007/0066628	A1	3/2007	Zhang et al.
2004/0213744	A1	10/2004	Lulla et al.	2007/0066637	A1	3/2007	Zhang et al.
2004/0234606	A1	11/2004	Levine et al.	2007/0066675	A1	3/2007	Zhang et al.
2004/0253319	A1	12/2004	Netke et al.	2007/0088029	A1	4/2007	Balog et al.
2004/0259817	A1	12/2004	Waldon et al.	2007/0093548	A1	4/2007	Diffendal et al.
2004/0266745	A1	12/2004	Schwanitz et al.	2007/0116729	A1	5/2007	Palepu
2005/0004088	A1	1/2005	Hesch	2007/0116829	A1	5/2007	Prakash et al.
2005/0009800	A1	1/2005	Thumbeck et al.	2007/0178166	A1	8/2007	Bernstein et al.
2005/0020552	A1	1/2005	Aschkenasay et al.	2007/0184558	A1	8/2007	Roth et al.
2005/0021009	A1	1/2005	Massara et al.	2007/0191319	A1	8/2007	Ke et al.
2005/0025833	A1	2/2005	Aschkenasay et al.	2007/0196433	A1	8/2007	Ron et al.
2005/0031651	A1	2/2005	Gervais et al.	2007/0207225	A1	9/2007	Squadrito
2005/0042173	A1	2/2005	Besse et al.	2007/0225281	A1	9/2007	Zhang et al.
2005/0042268	A1	2/2005	Aschkenasay et al.	2007/0238713	A1	10/2007	Gast et al.
2005/0048116	A1	3/2005	Straub et al.	2007/0243229	A1	10/2007	Smith et al.
2005/0079138	A1	4/2005	Chickering, III et al.	2007/0264309	A1	11/2007	Chollet et al.
2005/0085453	A1	4/2005	Govindarajan	2007/0264345	A1	11/2007	Eros et al.
				2007/0264349	A1	11/2007	Lee et al.
				2007/0286819	A1	12/2007	DeVries et al.
				2007/0287789	A1	12/2007	Jones et al.
				2007/0292387	A1	12/2007	Jon et al.



## US 8,846,649 B2

Page 5

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2008/0026035 A1 1/2008 Chollet et al.  
 2008/0026062 A1 1/2008 Farr et al.  
 2008/0038350 A1 2/2008 Gerecke et al.  
 2008/0085877 A1 4/2008 Bortz  
 2008/0095838 A1 4/2008 Abou Chacra-Vernet  
 2008/0113953 A1 5/2008 De Vries et al.  
 2008/0114050 A1 5/2008 Fensome et al.  
 2008/0119537 A1 5/2008 Zhang et al.  
 2008/0125402 A1 5/2008 Diliberti et al.  
 2008/0138379 A1 6/2008 Jennings-Spring  
 2008/0145423 A1 6/2008 Khan et al.  
 2008/0175814 A1 7/2008 Phiasivongsa et al.  
 2008/0188829 A1 8/2008 Creasy  
 2008/0206161 A1 8/2008 Tamarkin et al.  
 2008/0220069 A1 9/2008 Allison  
 2008/0234199 A1 9/2008 Katamreddym et al.  
 2008/0255078 A1 10/2008 Katamreddym et al.  
 2008/0255089 A1 10/2008 Katamreddym et al.  
 2008/0299220 A1 12/2008 Tamarkin et al.  
 2008/0306036 A1 12/2008 Katamreddy et al.  
 2008/0312197 A1 12/2008 Rodriguez  
 2008/0312198 A1 12/2008 Rodriguez  
 2008/0319078 A1 12/2008 Katamreddym et al.  
 2009/0053294 A1 2/2009 Prendergast  
 2009/0060982 A1 3/2009 Ron et al.  
 2009/0068118 A1 3/2009 Eini et al.  
 2009/0081278 A1 3/2009 De Graaff et al.  
 2009/0081303 A1 3/2009 Savoir et al.  
 2009/0092656 A1 4/2009 Klamerus et al.  
 2009/0099106 A1 4/2009 Phiasivongsa et al.  
 2009/0131385 A1 5/2009 Voskuhl  
 2009/0137478 A1 5/2009 Bernstein et al.  
 2009/0137538 A1 5/2009 Klamerus et al.  
 2009/0143344 A1 6/2009 Chang  
 2009/0181088 A1 7/2009 Song et al.  
 2009/0214474 A1 8/2009 Jennings  
 2009/0227025 A1 9/2009 Nichols et al.  
 2009/0232897 A1 9/2009 Sahoo et al.  
 2009/0258096 A1 10/2009 Cohen  
 2009/0264395 A1 10/2009 Creasy et al.  
 2009/0269403 A1 10/2009 Shaked et al.  
 2009/0285772 A1 11/2009 Phiasivongsa et al.  
 2009/0318558 A1 12/2009 Kim et al.  
 2009/0325916 A1 12/2009 Zhang et al.  
 2010/0028360 A1 2/2010 Atwood  
 2010/0040671 A1 2/2010 Ahmed et al.  
 2010/0048523 A1 2/2010 Bachman et al.  
 2010/0074959 A1 3/2010 Hansom et al.  
 2010/0086599 A1 4/2010 Huempel et al.  
 2010/0092568 A1 4/2010 Lerner et al.  
 2010/0105071 A1 4/2010 Laufer et al.  
 2010/0129320 A1 5/2010 Phiasivongsa et al.  
 2010/0136105 A1 6/2010 Chen et al.  
 2010/0137265 A1 6/2010 Leonard  
 2010/0137271 A1 6/2010 Chen et al.  
 2010/0152144 A1 6/2010 Hermsmeyer  
 2010/0168228 A1 7/2010 Bose et al.  
 2010/0183723 A1 7/2010 Laurent-Applegate  
 2010/0184736 A1 7/2010 Coelingh Bennink et al.  
 2010/0190758 A1 7/2010 Fauser et al.  
 2010/0240626 A1 9/2010 Kulkarni et al.  
 2010/0247632 A1 9/2010 Dong et al.  
 2010/0255085 A1 10/2010 Liu et al.  
 2010/0303825 A9 12/2010 Sirbasku et al.  
 2010/0312137 A1 12/2010 Gilmour et al.  
 2010/0316724 A1 12/2010 Whitfield et al.  
 2010/0330168 A1 12/2010 Gicquel et al.  
 2011/0028439 A1 2/2011 Witt-Enderby et al.  
 2011/0053845 A1 3/2011 Levine et al.  
 2011/0076775 A1 3/2011 Stewart et al.  
 2011/0076776 A1 3/2011 Stewart et al.  
 2011/0086825 A1 4/2011 Chatroux  
 2011/0091555 A1 4/2011 De Luigi Bruschi et al.  
 2011/0098631 A1 4/2011 McIntyre et al.  
 2011/0104289 A1 5/2011 Savoir Vilboeuf et al.

2011/0135719 A1 6/2011 Besins et al.  
 2011/0182997 A1 7/2011 Lewis et al.  
 2011/0195114 A1 8/2011 Carrara et al.  
 2011/0195944 A1 8/2011 Mura et al.  
 2011/0217341 A1 9/2011 Sah  
 2011/0250274 A1 10/2011 Shaked et al.  
 2011/0256092 A1 10/2011 Phiasivongsa et al.  
 2011/0262494 A1 10/2011 Achleitner et al.  
 2011/0268665 A1 11/2011 Tamarkin et al.  
 2011/0293720 A1 12/2011 General et al.  
 2011/0311592 A1 12/2011 Birbara  
 2011/0312927 A1 12/2011 Nachaegari et al.  
 2011/0312928 A1 12/2011 Nachaegari et al.  
 2012/0009276 A1 1/2012 De Groote  
 2012/0015350 A1 1/2012 Nabatiyan et al.  
 2012/0045532 A1 2/2012 Cohen  
 2012/0269878 A2 2/2012 Cantor et al.  
 2012/0052077 A1 3/2012 Truitt et al.  
 2012/0128625 A1 5/2012 Shalwitz et al.  
 2012/0128777 A1 5/2012 Keck et al.  
 2012/0149748 A1 6/2012 Shanler et al.  
 2012/0269721 A1 10/2012 Weng et al.  
 2012/0283671 A1 11/2012 Shibata et al.  
 2013/0022674 A1 1/2013 Dudley et al.  
 2013/0029947 A1 1/2013 Nachaegari et al.  
 2013/0129818 A1 5/2013 Bernick et al.

## FOREIGN PATENT DOCUMENTS

EP 0275716 A1 7/1988  
 EP 0622075 A1 11/1994  
 EP 0785211 A1 1/1996  
 EP 0811381 A1 6/1997  
 EP 0785212 A1 7/1997  
 EP 1094781 B1 7/2008  
 EP 2191833 A1 6/2010  
 GB 1589946 A1 2/1921  
 GB 452238 A 8/1936  
 GB 720561 A 12/1954  
 GB 848881 A 9/1960  
 GB 874368 A 8/1961  
 IN 216026 A 3/2008  
 IN 2005KO00053 A 9/2009  
 IN 244217 A 11/2010  
 WO 9011064 A1 10/1990  
 WO 9317686 A1 9/1993  
 WO 9422426 A1 10/1994  
 WO 9530409 A1 11/1995  
 WO 9609826 A2 4/1996  
 WO 9630000 A1 10/1996  
 WO 9705491 2/1997  
 WO 9743989 A1 11/1997  
 WO 9810293 A1 3/1998  
 WO 9832465 A1 7/1998  
 WO 9851280 A1 11/1998  
 WO 9932072 7/1999  
 WO 9939700 A1 8/1999  
 WO 9942109 A1 8/1999  
 WO 9943304 9/1999  
 WO 9948477 A1 9/1999  
 WO 9953910 A2 10/1999  
 WO 9963974 A2 12/1999  
 WO 0001351 A1 1/2000  
 WO 0006175 A1 2/2000  
 WO 0038659 A1 7/2000  
 WO 0045795 A2 8/2000  
 WO 0050007 A1 8/2000  
 WO 0059577 A1 10/2000  
 WO 0137808 A1 11/2000  
 WO 0076522 A1 12/2000  
 WO 0154699 A1 8/2001  
 WO 0160325 A1 8/2001  
 WO 0207700 A2 2/2002  
 WO 0211768 A1 2/2002  
 WO 0222132 A2 3/2002  
 WO 0240008 A2 5/2002  
 WO 02053131 A1 7/2002  
 WO 02078602 A2 10/2002  
 WO 02078604 A2 10/2002

## US 8,846,649 B2

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(56)

## References Cited

## FOREIGN PATENT DOCUMENTS

WO	03041718	A1	5/2003
WO	03041741	A1	5/2003
WO	03068186	A1	8/2003
WO	03077923	A1	9/2003
WO	03082254	A1	10/2003
WO	03092588	A2	11/2003
WO	2004017983	A1	3/2004
WO	2004032897	A2	4/2004
WO	2004052336	A2	6/2004
WO	2004054540	A2	7/2004
WO	2004080413	A2	9/2004
WO	2005027911	A1	3/2005
WO	2005030175	A1	4/2005
WO	2005087194	A1	9/2005
WO	2005087199	A2	9/2005
WO	2005105059	A1	11/2005
WO	2005115335	A1	12/2005
WO	2005120470	A1	12/2005
WO	2005120517	A1	12/2005
WO	2006013369	A2	2/2006
WO	2006034090	A1	3/2006
WO	2006036899	A2	4/2006
WO	2006053172	A2	5/2006
WO	2006105615	A1	10/2006
WO	2006113505	A2	10/2006
WO	2006138686	A1	12/2006
WO	2006138735	A2	12/2006
WO	2007045027	A1	4/2007
WO	2007103294	A2	9/2007
WO	2007123790	A1	11/2007
WO	2007124250	A2	11/2007
WO	2007144151	A1	12/2007
WO	2008049516	A3	5/2008
WO	2008152444	A2	12/2008
WO	2009002542	A1	12/2008
WO	2009036311	A1	3/2009
WO	2009040818	A2	4/2009
WO	2009069006	A2	6/2009
WO	2009098072	A2	8/2009
WO	2009133352	A2	11/2009
WO	2010033188	A2	3/2010
WO	2011000210	A1	1/2011
WO	2011073995	A2	6/2011
WO	2011120084	A1	10/2011
WO	2011128336	A1	10/2011
WO	2012009778	A2	1/2012
WO	2012024361	A1	2/2012
WO	2013192248	A1	12/2013
WO	2013192249	A1	12/2013
WO	2013192250	A1	12/2013
WO	2013192251	A1	12/2013

## OTHER PUBLICATIONS

International Search Report and Written Opinion for related International Application No. PCT/US13/046442 dated Nov. 1, 2013.  
 International Search Report and Written Opinion for related International Application No. PCT/US13/046443 dated Oct. 31, 2013.  
 International Search Report and Written Opinion for related International Application No. PCT/US13/046444 dated Oct. 31, 2013.  
 International Search Report and Written Opinion for related International Application No. PCT/US13/046445 dated Nov. 1, 2013.  
 USPTO; Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.  
 USPTO; Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002.  
 USPTO; Notice of Allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002.  
 Acarturk, "Mucoadhesive Vaginal Drug Delivery Systems," Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Exiler-Ankara, Recent Patents on Drug Delivery & Formulation 2009, 3, 193-205.  
 Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," Drug Development and Industrial Pharmacy, 35(5):525-547 (May 2009). Abstract Only.

Azure Pharma, Inc., "ELESTRIN™—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages. (Aug. 2009).  
 Bhavnani, et al., "Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ERA and ERB", Endocrinology, 149(10): 4857-4870 (Oct. 2008).  
 Bhavnani, et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," J Clin Endocrinol Metab, Mar. 2012, 97(3).  
 Tahition Noni, "Body Balance Cream," [http://products.tni.com/dominican\\_republic/sa\\_spanish/nonistore/product/3438/3416/](http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/), (undated), 1 page.  
 Nugen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, (undated), 3 pages.  
 Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," J. Kor. Pharm. Sci., 35(3):173-177, (2005).  
 Committee of Obstetric Practice, Committee Opinion—No. 522, Obstetrics & Gynecology, 119(4):879-882 (Apr. 2012).  
 Diramio, "Polyethylene Glycol Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia-Masters of Science Thesis, 131 pages. (2004). [http://athenaeum.libs.uga.edu/bitstream/handle/10724/7820/diramio\\_jackie\\_a\\_200412\\_ms.pdf?sequence=1](http://athenaeum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1).  
 Du, et al., "Percutaneous Progesterone Delivery Via Cream or Gel Application in Postmenopausal Women: A Randomized Cross-Over Study of Progesterone Levels in Serum, Whole Blood, Saliva, and Capillary Blood," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 11, (Feb. 2013).  
 Fotherby, K., "Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy," Contraception 1996;54:59-69.  
 Fuchs, et al., "The Effects of on Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," Pharmacology / Cosmetology, vol. 5, No. 1, 2006.  
 Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," International Journal of Pharmaceutics, 147(2):165-171 (Feb. 1997). Abstract Only.  
 Hargrove, et al., Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone, vol. 73, No. 4, pp. 606-612 Apr. 1989.  
 Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," Critical Reviews in Toxicology, 30(3):307-345 (2000).  
 Kincl, et al., "Increasing Oral Bioavailability of Progesterone by Formulation," Pergamon Press, Journal of Steroid Biochemistry, 1978, vol. 9, pp. 83-84.  
 Knuth et al., "Hydrogel Delivery Systems for Vaginal and Oral Applications: Formulation and Biological Considerations," Advanced Drug Delivery Reviews, 11(1-2):137-167 (Jul.-Aug. 1993). Abstract Only.  
 Lucy et al., "Gonadotropin-Releasing Hormone at Estrus: Luteinizing Hormone, Estradiol, and Progesterone During the Peri-estrus and Postinsemination Periods in Dairy Cattle," Biol Reprod. 35(2):300-311 (1986). Abstract Only.  
 Position Statement, "Management of Symptomatic Vulvovaginal Atrophy: 2013 Position Statement of the North American Menopause Society," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 9, pp. 888-902, Jun. 2013.  
 NuGest 900™, <http://www.thehormoneshop.net/nugest900.htm>, (undated), 4 pages.  
 Panay, et al., "The 2013 British Menopause Society & Women's Health Concern Recommendations on Hormone Replacement Therapy," DOI: 0.1177/1754045313489645, [min.sagepub.com](http://min.sagepub.com). Menopause International: The Integrated Journal of Postreproductive Health 0(0):1-10, 2013.  
 Panchagnula et al., "Development and Evaluation of an Intracutaneous Depot Formulation of Corticosteroids Using Transcutol as a Cosolvent: In-Vitro, Ex-Vivo and In-Vivo Rat Studies," J Pharm Pharmacol. 43(9):609-614 (Sep. 1991). Abstract Only.



## US 8,846,649 B2

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(56)

## References Cited

## OTHER PUBLICATIONS

Patel, et al., "Transdermal Drug Delivery System: A Review," *www.thepharmajournal.com*, vol. 1 No. 4 2012.

Salole, "The physiochemical properties of oestradiol," *Journal of Pharmaceutical & Biomedical Analysis*, 5 (7):635-648 (1987).

Sarrel, et al., "The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years," *American Journal of Public Health*, Published online ahead of print Jul. 18, 2013.

Shufelt, et al., "Hormone Therapy Dose, Formulation, Route of Delivery, and Risk of Cardiovascular Events in Women: Findings From the Women's Health Initiative Observational Study," *Menopause: The Journal of the North American Menopause Society*, vol. 21, No. 3, 2014.

Simon, et al., "Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet," *The American College of Obstetricians and Gynecologists*, vol. 112, No. 5, Nov. 2008.

Sitruk-Ware, et al., "Oral Micronized Progesterone," *Department of Reproductive Endocrinology*, vol. 36, No. 4, pp. 373-402, Oct. 1987.

Sitruk-Ware, et al., "Progestogens in Hormonal Replacement Therapy: New Molecules, Risks, and Benefits," *Menopause: The Journal of the North American Menopause Society*, vol. 9, No. 1, pp. 6-15, 2002.

Smith, et al., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens," *JAMA Internal Medicine* <http://archinte.jamanetwork.com>, Sep. 30, 2013.

Stanczyk, et al. "Ethinyl Estradiol and 17 $\beta$ -Estradiol in Combined Oral Contraceptives: Pharmacokinetics, Pharmacodynamics and Risk Assessment," *Departments of Obstetrics and Gynecology and Preventive Medicine, University of Southern California Keck School of Medicine, Contraception* 87 706-727, (2013).

Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," *Pharmaceutical Research*, 21(2):201-230 (Feb. 2004).

Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," *Skin Pharmacol Physiol*, 19:106-121 (2006). [http://www.nanobiotech.igim.unicamp.br/download/Trommer\\_skin%20penetration-2006rev.pdf](http://www.nanobiotech.igim.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf).

Whitehead, et al., "Absorption and Metabolism of Oral Progesterone," *The British Medical Journal*, vol. 280, No. 6217, Mar. 22, 1980.

Wood, et al., "Effects of Estradiol with Micronized Progesterone or Medroxyprogesterone Acetate on Risk Markers for Breast Cancer in Postmenopausal Monkeys," *Springer Science+Business Media B.V., Breast Cancer Res Treat* 101:125-134, (2007).

USPTO; Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545.

USPTO; Restriction/ Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562.

USPTO; Restriction/ Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623.

ACOG, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists, ACOG, No. 141, Vol. 123, No. 1, Jan. 2014, Obstetrics & Gynecology.

Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.

Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.

Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.

Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.

Bakmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.

Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, *Steroids*, vol. 46(6), pp. 967-974, Dec. 1985.

Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17 $\beta$ -estradiol and several A-ring . . . , *Vibrational Spectroscopy* 8, Elsevier, pp. 263, 1995.

Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, *Bollettino Chimico Farmaceutico*, vol. 122(1) pp. 20-26, 1983 SciFinder.

Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.

Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.

BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.

Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, *Acta Pharm. Jugosl.*, vol. 40 pp. 71-94, 1990.

Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.

Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, *Am J Obstet Gynecol*, vol. 180(6) part 1, pp. 1504-1511, 1999.

Busetta, Par Bernard, Structure Cristalline et Moleculaire du Complexe Oestradiol-Propanol, *Acta Cryst.*, B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.

Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, *Revista Mexicana de Fisica*, 50, Suplemento 1 pp. 1-3, 2004.

Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.

Commodari, Fernando, Comparison of 17 $\beta$ -estradiol structures from x-ray diffraction and solution NMR, *Magn. Reson. Chem.*, vol. 43, pp. 444-450, 2005, Wiley InterScience.

Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, *The Lancet*, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.

Dideberg, O, et al., Crystal data on progesterone (C<sub>21</sub>H<sub>30</sub>O<sub>2</sub>), desoxycorticosterone (C<sub>21</sub>H<sub>30</sub>O<sub>3</sub>), corticosterone (C<sub>21</sub>H<sub>30</sub>O<sub>4</sub>) and aldosterone . . . , *J. Appl. Cryst.* vol. 4 pp. 80, 1971.

Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , *Inter. Journal of Pharmaceutics*, Elsevier, vol. 363, pp. 40-49, 2009.

Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, *J. Am. Chem. Soc.*, vol. 103 pp. 6705-6712, Jun. 1981.

Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , *J. Thermal Anal.*, vol. 37 pp. 1869-1875, 1991, Wiley.

Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, SciFinder, *Pharmaceutica Acta Helvetiae*, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.

Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.

Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.

FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.

Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.

Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.

Giron, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, *Thermochimica Acta*, vol. 248 pp. 1-59, 1995, Elsevier.

(56)

**References Cited****OTHER PUBLICATIONS**

- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, *J. Pharmaceutical & Biomedical Anal.*, vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, *Acta Cryst.*, vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, *Pharm Res.*, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, *Jour. of Mag. Resonance*, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, *Mol. Pharmacology*, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, *Pharmaceutical Development and Tech.*, vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Idder, Salima, et al., Physicochemical properties of Progesterone, *SciFinder*, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johnson, William S, et al., Racemic Progesterone, *Tetrahedron Letters* No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, *Drug Dev. & Indus. Pharm.*, vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Korkmaz, Filiz, Biophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyar, P.N., Stability indicating HPTLC method for the estimation of estradiol, *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminiewski, R, et al., EPR Study of the Stable Radical in a  $\gamma$ -Irradiated Single Crystal of Progesterone, *Jour. of Mag. Resonance*, vol. 46 pp. 300-305, 1982, Academic Press.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, *Jour. of Mol. Structure, Theochem*, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, *Jour. of Mol. Structure, Theochem* vol. 425, pp. 171-179, 1998, Elsevier.
- Kuhnert-Brandstatter, M., Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , *Drug Development and Industrial Pharmacy, Informa Healthcare* vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steroids, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G., et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , *Maturitas, The European Menopaus Journal*, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroidal conformation of 17a- and 17B-estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17b and Progesterone Concentrations in Uterine Lymph and Systematic Blood . . . , *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, *Catalent Pharma Solutions*, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MONO1500003758.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B-Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Deliv. & Indust. Pharmacy*, 35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://lxsr7.oru.edu/~alang/onsc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res*, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, *Crystal Structure Comm., Intn'l Union of Crystallography*, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, *Schering Corporation*, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.

## US 8,846,649 B2

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(56)

## References Cited

## OTHER PUBLICATIONS

- Pisegna, Gisla L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012%20Patches\_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Salole, Eugene G., Estradiol, *Analytical Profiles of Drug Substances*, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Base . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, *SciFinder*, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- SciFinder Scholar Prednisone Chemical Properties, *SciFinder*, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, *SciFinder*, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, *SciFinder*, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), *Crystal Structure Comm.*, vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Saffey Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, Cas No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of Thevetia peruviana and *Hura crepitans* Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopoeia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index>[Feb. 3, 2014 1:37:50 PM].
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.
- Corn Refiners Assoc, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Eqbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Ferrari, Roseli AP., et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, Piracicaba, Braz.
- Gunstone, Frank D, et al., Vegetable Oils in Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, *Springerlink.com*, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science*, vol. 47, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Lauroyl Polyoxylglycerides, Saffey Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate-Corn Oil, Lot G0L404, Jul. 2013.
- Weber, E.J., Corn Lipids, *Cereal Chem.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.
- PCCA, Apothogram, May 2014, pp. 1-14, Houston, TX.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Stein, Emily A, et al., Progesterone Physical Properties, *SciFinder*, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone Physical Properties, *SciFinder*, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone, *SciFinder Scholar Search*, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Struhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , *SciFinder, Cesko-Slovenska Farmacie*, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, *Dept of Investigative Med., Univ. Cambridge, Gt. Britain* pp. 531-542, 1972.
- Takacs M, et al., The light sensitivity of corticosteroids in crystalline form, *Pharmaceutica acta Helvetica*, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S, et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC- MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , *Intl. J. of Pharmaceut.*, vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, *AAPS PharmSciTech*, vol. 11, No. 3, Sep. 2010.

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(56)

**References Cited**

**OTHER PUBLICATIONS**

USP Monographs: Progesterone, USP29, [www.pharmacopeia.cn/v29240/usp29nf24s0\\_m69870.html](http://www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html), search done: Feb. 25, 2014.

Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . Fertility and Sterility, vol. 75(6) pp. 1065, Jun. 2001.

Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, J. SteroidBiochem. Mol. Biol. (2013), Elsevier.

Wiranidchamong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, Thermochimica Acta 485, Elsevier, pp. 57, 2009.

Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, J. of Pharmaceutical Sciences, vol. 69(8) pp. 912-922, 1980.

Yalkowsky, Samuel H, Handbook of Aqueous Solubility Data, Solutions, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.

Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, Journal of Steroid Biochem & Mol Biology, vol. 86 pp. 477-486, 2003.

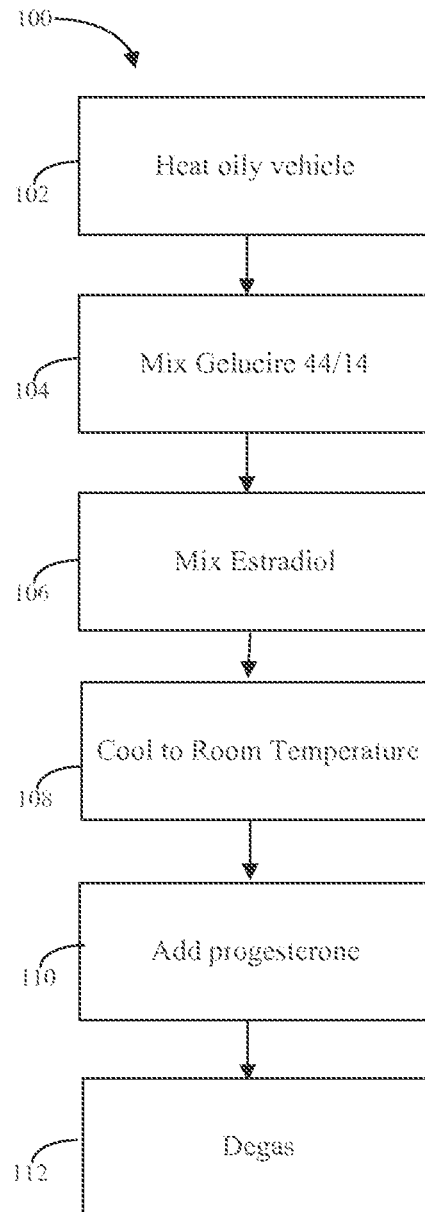
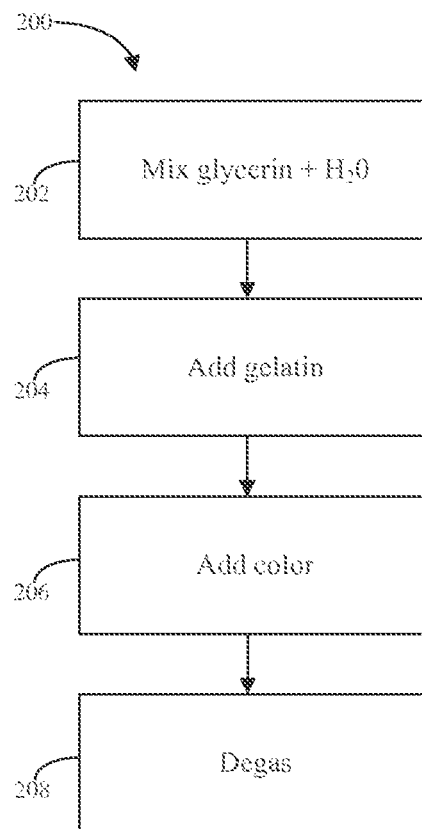


Fig. 1



**Fig. 2**

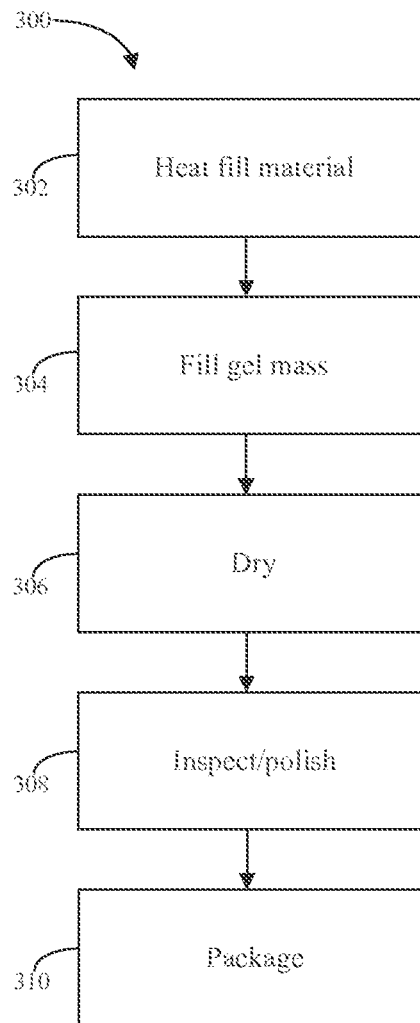


Fig. 3



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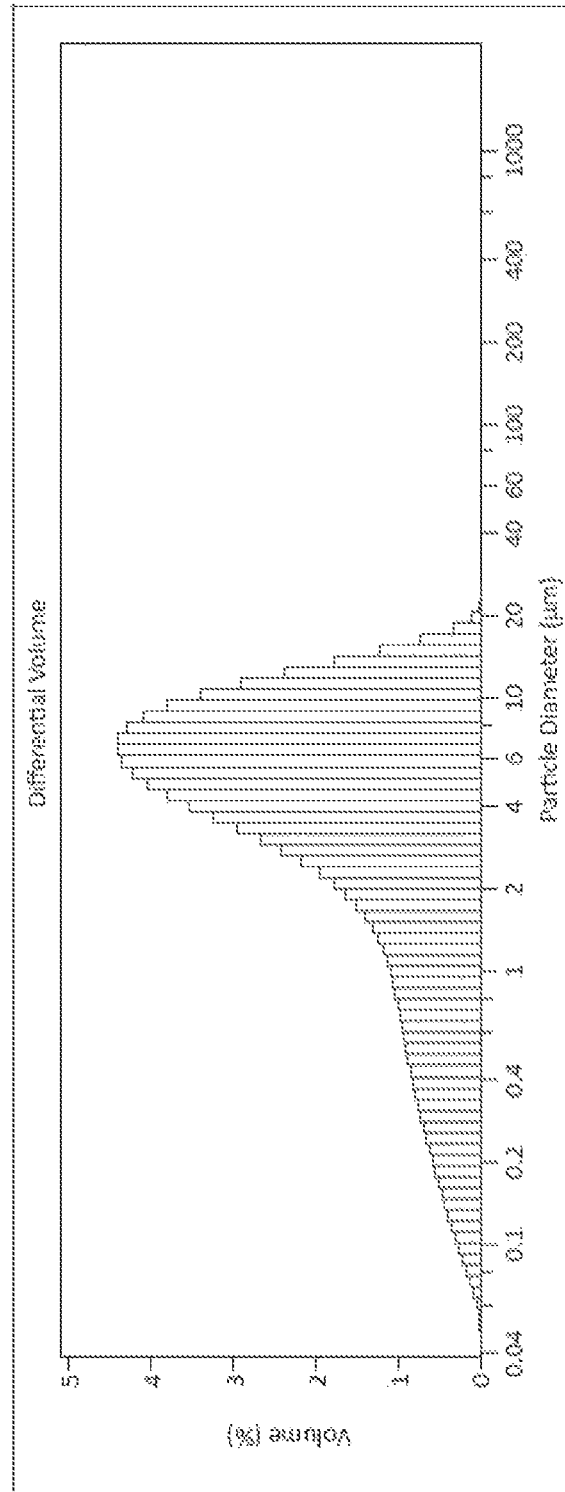


FIG. 4

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## NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

### CROSS REFERENCE TO RELATED APPLICATIONS

This application is a non-provisional application of and claims priority to the following U.S. Provisional patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

### BACKGROUND

#### 1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

#### 2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

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"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as PREM-PRO (conjugated estrogens/medroxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens plus medroxyprogesterone acetate tablets) (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN (conjugated estrogens tablets) (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

### SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

### BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

### DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

#### DEFINITIONS

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to PROMETRIUM (progesterone, USP) at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC,  $C_{max}$ , and optionally,  $T_{max}$ .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ $C_{max}$ ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ $T_{max}$ ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC,  $C_{max}$  and, optionally,  $T_{max}$  are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to estab-

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lished governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

#### DESCRIPTION

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM (progesterone, USP) when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg:50 mg to about 2 mg:1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

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Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of PROMETRIUM (progesterone, USP). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM (progesterone, USP) at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM (progesterone, USP) can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 $\beta$ -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/

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sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017  $\mu$ m to 2000  $\mu$ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4  $\mu$ m to 2000  $\mu$ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These



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formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE (a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride); SASOL Germany GMBH, Hamburg; MIGLYOL (caprylic/capric triglyceride) includes MIGLYOL 810 (Caprylic/Capric Triglyceride), MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 816 (Caprylic/Capric Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL PG-10 (Propylene Glycol Monocaprate); the CAPMUL brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM (Medium Chain Mono- and Diglycerides)); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL (diethylene glycol mono ester)); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL (caprylic/capric triglyceride); TRANSCUTOL (Diethylene glycol monoethyl ether), MIGLYOL (caprylic/capric triglyceride) and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant; and CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for full solubilization of progesterone. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride) can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

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Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxy-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may

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comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from errone-

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ous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

## EXAMPLES

### Example 1

#### Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF)	141
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	31.2

\*Literature reference - Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

### Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) at 50%; and also CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL PG-8 (Propylene Glycol Monocaprylate) mixed with MIGLYOL (caprylic/capric triglyceride) at the 15 and 30% level did not provide sufficient solubility.

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TABLE 2

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (85:15)	4.40
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	8.60
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	>12
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	>12
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	14.0
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	19.8
Polysorbate 80:CAPMUL MCM (Medium Chain Mono- and Diglycerides) (20:80)	15.0

## Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. MIGLYOL 812 (Caprylic/Capric Triglyceride) with 4% TRANSCUTOL (Diethylene glycol monoethyl ether) precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL (caprylic/capric triglyceride): CAPMUL (a propylene glycol monocaprylate; propylene glycol monocaprylate) blends at 30 and 50% or in CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride) (4:96)	4	Crystallizes after 96 hours
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	6	Clear, after 14 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	6	Clear, after 14 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	6	Clear after 14 days

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12 mg estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) 50:50, CAPMUL MCM (Medium Chain Mono- and Diglycerides), and in mixtures of TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Clear, after 12 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear after 12 days

## Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization. All CAPMUL PG-8 (Propylene Glycol Monocaprylate) containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL PG-8 (Propylene Glycol Monocaprylate) alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25)	6	Precipitated
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate)	12	Hazy



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TABLE 5-continued

Formulation	Estradiol mg/g	Results after addition of 7% water
Monocaprylate) (50:50)		
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Hazy
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

## Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF))	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

## Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/ triglycerides of caprylic/capric	322.97	99.38	3.23 kg

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TABLE 8-continued

Ingredient	Mg/Capsule	% w/w	Amount/Batch
acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))			
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved.

## Example 7

## Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL (caprylic/capric triglyceride) was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL (caprylic/capric triglyceride) may be used in embodiments comprising a suspension of progesterone, though MIGLYOL (caprylic/capric triglyceride), standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM (Medium Chain Mono- and Diglycerides) is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL (caprylic/capric triglyceride) had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL MCM (Medium Chain Mono- and Diglycerides). It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL MCM (Medium Chain Mono- and Diglycerides).

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	73.4
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	95
MIGLYOL 812 (Caprylic/ Capric Triglyceride)	27.8

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In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM (Medium Chain Mono- and Diglycerides) in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Gelucire 44/14 system, wherein the ratio of CAPMUL MCM (Medium Chain Mono- and Diglycerides) to GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (9:1)	86.4
CAPMUL MCM (Medium Chain Mono- and Diglycerides) GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (7:3)	70.5
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (6:4)	57.4

## Example 7

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97
GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL MCM (Medium Chain Mono- and Diglycerides) may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to

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40° C. +/-2° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) may be added to the CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Heat may be removed from the GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

## Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL (caprylic/capric triglyceride) is heated to about 45° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/ diglycerides/ triglycerides of caprylic/capric acid	394.0	65.67	Carrier	3.94

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TABLE 13-continued

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
(CAPMUL MCM (Medium Chain Mono- and Diglycerides)) Lauroyl polyoxyl-32- glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to about 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/ Capric Triglyceride) or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL (caprylic/capric triglyceride) may be present in a range from about 35-95% by weight; GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10

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mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279  $\mu$ m, an X75 of 7.442  $\mu$ m, and an X25 of 1.590  $\mu$ m. The Beckman Device also yielded that the mean particle size is 4.975  $\mu$ m, the median particle size is 4.279  $\mu$ m, the mode particle size is 6.453  $\mu$ m, and the standard deviation is 3.956  $\mu$ m. A graph of the particle distribution obtained is shown in FIG. 4.

## Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0  $\mu$ m, an X75 of 17.3  $\mu$ m, and an X25 of 5.3  $\mu$ m. The Beckman Device also yielded that the mean particle size is 11.8  $\mu$ m, the median particle size is 11.04  $\mu$ m, the mode particle size is 13.6  $\mu$ m, and the standard deviation is 7.8  $\mu$ m.

## Example 12

In order to increase the solubility of progesterone in the final solution, GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97	5.78
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 40° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

## Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

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TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL MCM (Medium Chain Mono-and Diglycerides), NF		73.371	146.74	1467.42
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.500	3.00	30.00
Total:			100.000	200.00 mg	2000.00

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	CAPMUL MCM (Medium Chain Mono-and Diglycerides), NF		65.32	391.93	3919.3
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The

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mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 15

## Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM (progesterone, USP) (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM (progesterone, USP) soft gel Capsule 200 mg and ESTRACE (estradiol vaginal cream, USP, 0.01%) (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient tem-



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perature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of  $-70^{\circ}\text{C} \pm 20^{\circ}\text{C}$  in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

#### Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to  $40^{\circ}\text{C} \pm 5^{\circ}\text{C}$ . Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ .

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

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With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Heating may be performed until the temperature reaches  $80^{\circ}\text{C} \pm 5^{\circ}\text{C}$ .

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to  $30^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes. Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of  $55^{\circ}\text{C} \pm 10^{\circ}\text{C}$ . The wedge temperature may be  $38^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . The drum cooling temperature may be  $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$ . The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness  $0.85\text{ mm} \pm 0.05\text{ mm}$  using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight  $\pm 5\%$  (i.e.,  $650 \pm 33\text{ mg}$  and  $325 \pm 16.3\text{ mg}$ ).

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of  $55^{\circ}\text{C} \pm 10^{\circ}\text{C}$ . The wedge temperature may be  $38^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . The drum cooling temperature may be  $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$ . The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness  $0.85\text{ mm} \pm 0.05\text{ mm}$  using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight  $\pm 5\%$  (i.e.,  $650 \pm 33\text{ mg}$  and  $325 \pm 16.3\text{ mg}$ ).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl

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alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A pharmaceutical composition comprising:  
solubilized estradiol;  
suspended progesterone;  
and a solubilizing agent;  
wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;  
wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and  
wherein the solubilizing agent comprises an effective amount of at least one of mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid.
2. The pharmaceutical composition of claim 1, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.
3. The pharmaceutical composition of claim 1, wherein the formulation is formulated as a gelatin capsule.
4. The pharmaceutical composition of claim 1, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.
5. The pharmaceutical composition of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.
6. A pharmaceutical composition comprising:  
solubilized estradiol;  
suspended progesterone; and  
a solubilizing agent, the solubilizing agent comprising an effective amount of mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid;  
wherein the estradiol and the suspended progesterone are present in the solubilizing agent the estradiol and progesterone are uniformly dispersed, and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

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wherein the estradiol does not precipitate for at least 14 days.

7. The pharmaceutical composition of claim 6, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

8. The pharmaceutical composition of claim 6, wherein the composition is formulated as a gelatin capsule.

9. The pharmaceutical composition of claim 6, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

10. The pharmaceutical composition of claim 6, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

11. A method of treating menopause symptoms of a woman with a uterus comprising:

administering an effective amount of a pharmaceutical composition, the pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent,

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises an effective amount of at least one of mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid.

12. The method of claim 11, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

13. The method of claim 11, wherein the composition is formulated in a gelatin capsule.

14. The method of claim 11, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

15. The method of claim 11, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,846,649 B2  
APPLICATION NO. : 14/099571  
DATED : September 30, 2014  
INVENTOR(S) : Brian A. Bernick et al.

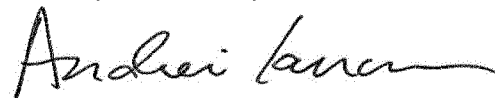
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this  
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu  
*Director of the United States Patent and Trademark Office*



# EXHIBIT D



US008987237B2

(12) **United States Patent**  
**Bernick et al.**

(10) **Patent No.:** **US 8,987,237 B2**  
(45) **Date of Patent:** **\*Mar. 24, 2015**

(54) **NATURAL COMBINATION HORMONE  
REPLACEMENT FORMULATIONS AND  
THERAPIES**

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(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-  
claimer.

3,478,070	A	11/1969	Smith et al.
3,526,648	A	9/1970	Bertin et al.
3,710,795	A	1/1973	Higuchi et al.
3,729,560	A	4/1973	Hagerman
3,729,566	A	4/1973	Ericsson et al.
3,755,573	A	8/1973	Berman
3,755,575	A	8/1973	Lerner
3,903,880	A	9/1975	Higuchi et al.
3,916,898	A	11/1975	Robinson
3,916,899	A	11/1975	Theeuwes et al.
3,921,636	A	11/1975	Zaffaroni
3,923,997	A	12/1975	Meuly
3,948,254	A	4/1976	Zaffaroni
3,971,367	A	7/1976	Zaffaroni
3,977,404	A	8/1976	Theeuwes
3,993,072	A	11/1976	Zaffaroni
4,008,719	A	2/1977	Theeuwes
4,012,496	A	3/1977	Schopflin et al.
4,014,334	A	3/1977	Theeuwes et al.
4,014,987	A	3/1977	Heller et al.
4,016,251	A	4/1977	Higuchi et al.
4,071,623	A	1/1978	Van Der Vies
4,093,709	A	6/1978	Choi
4,154,820	A	5/1979	Simoons
4,155,991	A	5/1979	Schopflin et al.
4,196,188	A	4/1980	Besins
4,215,691	A	8/1980	Wong

(Continued)

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(51) **Int. Cl.**

**A01N 45/00** (2006.01)

**A61K 9/48** (2006.01)

**A61K 9/70** (2006.01)

**A61K 9/16** (2006.01)

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**A61K 31/57** (2006.01)

(52) **U.S. Cl.**

CPC ..... **A61K 9/7023** (2013.01); **A61K 9/16**  
(2013.01); **A61K 31/565** (2013.01); **A61K**  
**31/57** (2013.01); **A61K 9/4858** (2013.01)

USPC ..... **514/169**; 424/452

(58) **Field of Classification Search**

CPC ..... **A61K 31/56**  
See application file for complete search history.

(56) **References Cited**

#### U.S. PATENT DOCUMENTS

1,967,351	A	7/1934	Doisy
2,232,438	A	2/1941	Butenandt
2,379,832	A	7/1945	Serini et al.
2,649,399	A	8/1953	Grant et al.
3,198,707	A	8/1965	Nomaine et al.

#### FOREIGN PATENT DOCUMENTS

BR	PI 1001367-9	A2	7/2012
CN	102258455	A	11/2011

(Continued)

#### OTHER PUBLICATIONS

International Search Report and Written Opinion for related Interna-  
tional Application No. PCT/US12/066406 dated Jan. 24, 2013.

International Search Report and Written Opinion for related Interna-  
tional Application No. PCT/US13/023309 dated Apr. 9, 2013.

International Search Report and Written Opinion for related Interna-  
tional Application No. PCT/US13/046442 dated Nov. 1, 2013.

International Search Report and Written Opinion for related Interna-  
tional Application No. PCT/US13/046443 dated Oct. 31, 2013.

International Search Report and Written Opinion for related Interna-  
tional Application No. PCT/US13/046444 dated Oct. 31, 2013.

International Search Report and Written Opinion for related Interna-  
tional Application No. PCT/US13/046445 dated Nov. 1, 2013.

USPTO; Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl.  
No. 13/684,002.

(Continued)

*Primary Examiner* — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend &  
Stockton LLP

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are pro-  
vided herein. Among others, the following formulations are  
provided herein: solubilized estradiol without progesterone;  
micronized progesterone without estradiol; micronized  
progesterone with partially solubilized progesterone; solubi-  
lized estradiol with micronized progesterone; solubilized  
estradiol with micronized progesterone in combination with  
partially solubilized progesterone; and solubilized estradiol  
with solubilized progesterone.

**20 Claims, 4 Drawing Sheets**

## US 8,987,237 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

4,237,885	A	12/1980	Wong	5,676,968	A	10/1997	Lipp et al.
4,310,510	A	1/1982	Sherman et al.	5,677,292	A	10/1997	Li et al.
4,327,725	A	5/1982	Cortese et al.	5,686,097	A	11/1997	Taskovich et al.
4,372,951	A	2/1983	Vorys	5,693,335	A	12/1997	Xia et al.
4,384,096	A	5/1983	Sonnabend	5,694,947	A	12/1997	Lehtinen et al.
4,393,871	A	7/1983	Vorhauer	5,700,480	A	12/1997	Hille et al.
4,402,695	A	9/1983	Wong	5,709,844	A	1/1998	Arbeit et al.
4,423,151	A	12/1983	Baranczuk	5,719,197	A	2/1998	Kanios et al.
4,449,980	A	5/1984	Millar et al.	5,735,801	A	4/1998	Caillouette
4,610,687	A	9/1986	Fogwell	5,739,176	A	4/1998	Dunn et al.
4,629,449	A	12/1986	Wong	5,744,463	A	4/1998	Bair
4,732,763	A	3/1988	Beck et al.	5,747,058	A	5/1998	Tipton et al.
4,738,957	A	4/1988	Laurent et al.	5,762,614	A	6/1998	Caillouette
4,756,907	A	7/1988	Beck et al.	5,770,176	A	6/1998	Nargessi
4,762,717	A	8/1988	Crowley	5,770,219	A	6/1998	Chiang et al.
4,788,062	A	11/1988	Gale et al.	5,770,220	A	6/1998	Meconi et al.
4,816,257	A	3/1989	Buster et al.	5,770,227	A	6/1998	Dong et al.
4,822,616	A	4/1989	Zimmermann et al.	5,776,495	A	7/1998	Duclos et al.
4,865,848	A	9/1989	Cheng et al.	5,780,044	A	7/1998	Yewey et al.
4,900,734	A	2/1990	Maxson et al.	5,780,050	A	7/1998	Jain et al.
4,906,475	A	3/1990	Kim	5,788,980	A	8/1998	Nabahi
4,942,158	A	7/1990	Sarpotdar et al.	5,788,984	A	8/1998	Guenther et al.
4,961,931	A	10/1990	Wong	5,789,442	A	8/1998	Garfield et al.
5,030,629	A	7/1991	Rajadhyaksha	5,811,416	A	9/1998	Chwalisz
5,064,654	A	11/1991	Berner et al.	5,811,547	A	9/1998	Nakamichi et al.
5,108,995	A	4/1992	Casper	5,814,329	A	9/1998	Shah
5,128,138	A	7/1992	Blank	5,820,878	A	10/1998	Hirano et al.
5,130,137	A	7/1992	Crowley	5,827,200	A	10/1998	Caillouette
5,140,021	A	8/1992	Maxson et al.	5,840,327	A	11/1998	Gale et al.
5,211,952	A	5/1993	Pike et al.	5,843,468	A	12/1998	Burkoth et al.
5,252,334	A	10/1993	Chiang et al.	5,843,979	A	12/1998	Wille et al.
5,280,023	A	1/1994	Ehrlich et al.	5,858,394	A	1/1999	Lipp et al.
5,288,496	A	2/1994	Lewis	5,863,552	A	1/1999	Yue
5,340,584	A	8/1994	Spicer et al.	5,866,603	A	2/1999	Li et al.
5,340,585	A	8/1994	Pike et al.	5,882,676	A	3/1999	Lee et al.
5,340,586	A	8/1994	Pike et al.	5,885,612	A	3/1999	Meconi et al.
5,362,497	A	11/1994	Yamada et al.	5,888,533	A	3/1999	Dunn
5,382,573	A	1/1995	Casper	5,891,462	A	4/1999	Carrara
5,393,528	A	2/1995	Staab	5,891,868	A	4/1999	Cummings et al.
5,393,529	A	2/1995	Hoffmann et al.	5,898,038	A	4/1999	Yallampalli et al.
5,419,910	A	5/1995	Lewis	5,902,603	A	5/1999	Chen et al.
5,468,736	A	11/1995	Hodgen	5,904,931	A	5/1999	Lipp et al.
5,474,783	A	12/1995	Miranda et al.	5,906,830	A	5/1999	Farinas et al.
5,480,776	A	1/1996	Dullien	5,912,010	A	6/1999	Wille et al.
5,514,673	A	5/1996	Heckenmuller et al.	5,916,176	A	6/1999	Caillouette
5,516,528	A	5/1996	Hughes et al.	RE36,247	E	7/1999	Plunkett et al.
5,527,534	A	6/1996	Myhling	5,919,477	A	7/1999	Bevan et al.
5,529,782	A	6/1996	Staab	5,922,349	A	7/1999	Elliesen et al.
5,538,736	A	7/1996	Hoffmann et al.	5,928,666	A	7/1999	Farinas et al.
5,543,150	A	8/1996	Bologna et al.	5,942,243	A	8/1999	Shah
5,547,948	A	8/1996	Barcomb	5,952,000	A	9/1999	Venkateshwaran et al.
5,556,635	A	9/1996	Istin et al.	5,958,446	A	9/1999	Miranda et al.
5,565,199	A	10/1996	Page et al.	5,962,445	A	10/1999	Stewart
5,567,831	A	10/1996	Li	5,968,919	A	10/1999	Samour et al.
5,569,652	A	10/1996	Beier et al.	5,972,372	A	10/1999	Saleh et al.
5,580,572	A	12/1996	Mikler et al.	5,985,311	A	11/1999	Cordes et al.
5,582,592	A	12/1996	Kendrick	5,985,850	A	11/1999	Falk et al.
5,585,370	A	12/1996	Casper	5,985,861	A	11/1999	Levine et al.
5,595,759	A	1/1997	Wright et al.	5,989,568	A	11/1999	Breton et al.
5,595,970	A	1/1997	Garfield et al.	5,993,856	A	11/1999	Ragavan et al.
5,605,702	A	2/1997	Teillaud et al.	6,001,846	A	12/1999	Edwards et al.
5,607,691	A	3/1997	Hale et al.	6,007,835	A	12/1999	Bon-Lapillonne et al.
5,607,693	A	3/1997	Bonte et al.	6,010,715	A	1/2000	Wick et al.
5,609,617	A	3/1997	Shealy et al.	6,013,276	A	1/2000	Math et al.
5,620,705	A	4/1997	Dong et al.	6,022,562	A	2/2000	Autant et al.
5,626,866	A	5/1997	Ebert et al.	6,024,974	A	2/2000	Li
5,629,021	A	5/1997	Wright	6,024,976	A	2/2000	Miranda et al.
5,633,011	A	5/1997	Dong et al.	6,028,057	A	2/2000	Burns
5,633,242	A	5/1997	Ottel et al.	6,030,948	A	2/2000	Mann
5,639,743	A	6/1997	Kaswan et al.	6,039,968	A	3/2000	Nabahi
5,653,983	A	8/1997	Meybeck et al.	6,040,340	A	3/2000	Chwalisz et al.
5,656,286	A	8/1997	Miranda et al.	6,056,972	A	5/2000	Hermesmyer
5,660,839	A	8/1997	Allec et al.	6,060,077	A	5/2000	Meignant
5,662,927	A	9/1997	Ehrlich et al.	6,068,853	A	5/2000	Giannos et al.
5,663,160	A	9/1997	Meybeck et al.	6,074,625	A	6/2000	Hawthorne et al.
				6,077,531	A	6/2000	Salin-Drouin
				6,080,118	A	6/2000	Blythe
				6,083,178	A	7/2000	Caillouette
				6,086,916	A	7/2000	Agnus et al.

## US 8,987,237 B2

Page 3

(56)

## References Cited

## U.S. PATENT DOCUMENTS

6,087,352 A	7/2000	Trout	6,503,896 B1	1/2003	Tanabe et al.
6,090,404 A	7/2000	Meconi et al.	6,511,969 B1	1/2003	Hermismeyer
6,096,338 A	8/2000	Lacy et al.	6,521,250 B2	2/2003	Meconi et al.
6,106,848 A	8/2000	Preuill et al.	6,526,980 B1	3/2003	Tracy et al.
6,117,446 A	9/2000	Place	6,528,094 B1	3/2003	Savoir et al.
6,117,450 A	9/2000	Dittgen et al.	6,531,149 B1	3/2003	Kirstgen et al.
6,124,362 A	9/2000	Bradbury et al.	6,537,580 B1	3/2003	Savoir et al.
6,133,251 A	10/2000	Dittgen et al.	6,538,039 B2	3/2003	Laurent
6,133,320 A	10/2000	Yallampalli et al.	6,544,196 B2	4/2003	Caillouette
6,139,868 A	10/2000	Hoffmann	6,544,553 B1	4/2003	Hsia et al.
6,139,873 A	10/2000	Hughes, Jr. et al.	6,548,053 B1	4/2003	Stewart et al.
6,149,935 A	11/2000	Chiang et al.	6,548,491 B2	4/2003	Tanabe et al.
6,153,216 A	11/2000	Cordes et al.	6,551,611 B2	4/2003	Elliesen et al.
6,165,491 A	12/2000	Grasset et al.	6,555,131 B1	4/2003	Wolff et al.
6,165,975 A	12/2000	Adams et al.	6,562,367 B1	5/2003	Wolff et al.
6,187,323 B1	2/2001	Aiache et al.	6,562,370 B2	5/2003	Luo et al.
6,187,339 B1	2/2001	de Haan et al.	6,562,790 B2	5/2003	Chein
6,190,331 B1	2/2001	Caillouette	6,569,463 B2	5/2003	Patel et al.
6,201,072 B1	3/2001	Rathi et al.	6,583,129 B1	6/2003	Mazer et al.
6,217,886 B1	4/2001	Onyueksel et al.	6,586,006 B2	7/2003	Roser et al.
6,225,297 B1	5/2001	Stockemann et al.	6,589,549 B2	7/2003	Shih et al.
6,227,202 B1	5/2001	Matapurkar	6,593,317 B1	7/2003	De Ziegler et al.
6,228,383 B1	5/2001	Hansen et al.	6,599,519 B1	7/2003	Seo et al.
6,228,852 B1	5/2001	Shaak	6,610,652 B2	8/2003	Adams et al.
6,242,509 B1	6/2001	Berger et al.	6,610,670 B2	8/2003	Backensfeld et al.
6,245,811 B1	6/2001	Horrobin et al.	6,610,674 B1	8/2003	Schreiber
6,262,115 B1	7/2001	Guittard et al.	6,635,274 B1	10/2003	Masiz et al.
6,267,984 B1	7/2001	Beste et al.	6,638,528 B1	10/2003	Kanios
6,274,165 B1	8/2001	Meconi et al.	6,638,536 B2	10/2003	Savoir et al.
6,277,418 B1	8/2001	Markaverich et al.	6,645,528 B1	11/2003	Straub et al.
6,283,927 B1	9/2001	Caillouette	6,649,155 B1	11/2003	Dunlop et al.
6,287,588 B1	9/2001	Shih et al.	6,653,298 B2	11/2003	Potter et al.
6,287,693 B1	9/2001	Savoir et al.	6,656,929 B1	12/2003	Agnus et al.
6,294,188 B1	9/2001	Ragavan et al.	6,660,726 B2	12/2003	Hill et al.
6,294,192 B1	9/2001	Patel et al.	6,663,608 B2	12/2003	Rathbone et al.
6,294,550 B1	9/2001	Place et al.	6,663,895 B2	12/2003	Savoir et al.
6,299,900 B1	10/2001	Reed et al.	6,682,757 B1	1/2004	Wright
6,303,132 B1	10/2001	Nelson	6,692,763 B1	2/2004	Cummings et al.
6,303,588 B1	10/2001	Danielov	6,708,822 B1	3/2004	Muni
6,306,841 B1	10/2001	Place et al.	6,720,001 B2	4/2004	Chen et al.
6,306,914 B1	10/2001	Ziegler et al.	6,740,333 B2	5/2004	Beckett et al.
6,309,669 B1	10/2001	Setterstrom et al.	6,743,448 B2	6/2004	Kryger
6,309,848 B1	10/2001	Howett et al.	6,743,815 B2	6/2004	Huebner et al.
6,312,703 B1	11/2001	Orthofer	6,747,018 B2	6/2004	Tanabe et al.
6,328,987 B1	12/2001	Marini	6,750,291 B2	6/2004	Kim et al.
6,342,491 B1	1/2002	Dey et al.	6,756,208 B2	6/2004	Griffin et al.
6,344,211 B1	2/2002	Hille	6,776,164 B2	8/2004	Bunt et al.
6,372,209 B1	4/2002	Chrisope	6,787,152 B2	9/2004	Kirby et al.
6,372,245 B1	4/2002	Bowman et al.	6,805,877 B2	10/2004	Massara et al.
6,372,246 B1	4/2002	Wei	6,809,085 B1	10/2004	Elson et al.
6,387,390 B1	5/2002	Deaver et al.	6,818,226 B2	11/2004	Reed et al.
6,402,705 B1	6/2002	Caillouette	6,821,524 B2	11/2004	Marini
6,416,778 B1	7/2002	Ragavan et al.	6,841,716 B1	1/2005	Tsutsumi
6,420,352 B1	7/2002	Knowles	6,844,334 B2	1/2005	Hill et al.
6,423,039 B1	7/2002	Rathbone et al.	6,855,703 B1	2/2005	Hill et al.
6,423,683 B1	7/2002	Heaton et al.	6,860,859 B2	3/2005	Mehrotra et al.
6,432,438 B1	8/2002	Shukla	6,866,865 B2	3/2005	Hsia et al.
6,436,633 B1	8/2002	Kreider et al.	6,869,969 B2	3/2005	Huebner et al.
6,440,454 B1	8/2002	Santoro et al.	6,878,518 B2	4/2005	Whitehead
6,444,224 B1	9/2002	Rathbone et al.	6,901,278 B1	5/2005	Notelovitz
6,444,234 B1	9/2002	Kirby et al.	6,905,705 B2	6/2005	Palm et al.
6,451,300 B1	9/2002	Dunlop et al.	6,911,211 B2	6/2005	Eini et al.
6,451,339 B2	9/2002	Patel et al.	6,911,438 B2	6/2005	Wright
6,451,779 B1	9/2002	Hesch	6,923,988 B2	8/2005	Patel et al.
6,455,246 B1	9/2002	Howell et al.	6,924,274 B2	8/2005	Lardy et al.
6,455,517 B1	9/2002	Tanabe et al.	6,932,983 B1	8/2005	Straub et al.
6,465,004 B1	10/2002	Rossi-Montero et al.	6,939,558 B2	9/2005	Massara et al.
6,465,005 B1	10/2002	Biali et al.	6,943,021 B2	9/2005	Klausner et al.
6,465,006 B1	10/2002	Zhang et al.	6,958,327 B1	10/2005	Hillisch et al.
6,468,526 B2	10/2002	Chrisope	6,960,337 B2	11/2005	Daniels et al.
6,469,016 B1	10/2002	Place et al.	6,962,691 B1	11/2005	Lulla et al.
6,472,434 B1	10/2002	Place et al.	6,962,908 B2	11/2005	Aloba et al.
6,479,232 B1	11/2002	Howett et al.	6,967,194 B1	11/2005	Matsuo et al.
6,495,160 B2	12/2002	Esposito et al.	6,974,569 B2	12/2005	Dunlop et al.
6,500,814 B1	12/2002	Hesch	6,977,250 B2	12/2005	Rodriguez
			6,978,945 B2	12/2005	Wong et al.
			6,995,149 B1	2/2006	Endrikat et al.
			7,004,321 B1	2/2006	Palm et al.
			7,005,429 B2	2/2006	Dey et al.

## US 8,987,237 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

7,011,846 B2	3/2006	Shojaei et al.	7,862,552 B2	1/2011	McIntyre et al.
7,018,992 B2	3/2006	Koch et al.	7,867,990 B2	1/2011	Schultz et al.
7,030,104 B2	4/2006	Gray et al.	7,871,643 B2	1/2011	Lizio et al.
7,030,157 B2	4/2006	Ke et al.	7,879,830 B2	2/2011	Wiley
RE39,104 E	5/2006	Duclos et al.	7,884,093 B2	2/2011	Creasy et al.
7,074,779 B2	7/2006	Sue et al.	7,939,104 B2	5/2011	Barbera et al.
7,083,590 B1	8/2006	Bunt et al.	7,943,602 B2	5/2011	Bunschoten et al.
7,091,213 B2	8/2006	Metcalfe, III et al.	7,943,604 B2	5/2011	Coelingh Bennik et al.
7,094,228 B2	8/2006	Zhang et al.	7,960,368 B2	6/2011	Nickisch et al.
7,097,853 B1	8/2006	Garbe et al.	7,989,436 B2	8/2011	Hill et al.
7,101,342 B1	9/2006	Caillouette	7,989,487 B2	8/2011	Welsh et al.
7,105,573 B2	9/2006	Krajcik et al.	8,022,053 B2	9/2011	Mueller et al.
7,135,190 B2	11/2006	Piao et al.	8,048,017 B2	11/2011	Xu
7,153,522 B1	12/2006	Ikeura et al.	8,048,869 B2	11/2011	Bunschoten et al.
7,163,681 B2	1/2007	Giles-Komar	8,063,030 B2	11/2011	Ellman
7,163,699 B2	1/2007	Besse	8,071,576 B2	12/2011	Coelingh Bennink et al.
7,175,850 B2	2/2007	Cevc	8,071,729 B2	12/2011	Giles-Komar et al.
7,179,799 B2	2/2007	Hill et al.	8,075,916 B2	12/2011	Song et al.
7,196,074 B2	3/2007	Blye et al.	8,075,917 B2	12/2011	Chung et al.
7,198,800 B1	4/2007	Ko	8,076,317 B2	12/2011	Kulmann
7,198,801 B2	4/2007	Carrara et al.	8,076,319 B2	12/2011	Leonard
7,226,910 B2	6/2007	Wilson et al.	8,080,553 B2	12/2011	Keith et al.
7,247,625 B2	7/2007	Zhang et al.	8,088,605 B2	1/2012	Beaudet et al.
7,250,446 B2	7/2007	Sangita et al.	8,096,940 B2	1/2012	Josephson et al.
7,267,829 B2	9/2007	Kirby et al.	8,101,209 B2	1/2012	Legrand et al.
7,300,926 B2	11/2007	Prokai et al.	8,101,773 B2	1/2012	Smith
7,303,763 B2	12/2007	Ho	8,114,152 B2	2/2012	Furst
7,317,037 B2	1/2008	Fensome et al.	8,114,434 B2	2/2012	Sasaki et al.
7,329,654 B2	2/2008	Kanojia et al.	8,114,442 B2	2/2012	Tucker et al.
7,335,650 B2	2/2008	Potter et al.	8,119,741 B2	2/2012	Pavlin
7,374,779 B2	5/2008	Chen et al.	8,124,118 B2	2/2012	Lennernaes et al.
7,378,404 B2	5/2008	Peters	8,124,595 B2	2/2012	Boissonneault
7,381,427 B2	6/2008	Ancira et al.	8,147,561 B2	4/2012	Binmoeller
7,387,789 B2	6/2008	Klose et al.	8,148,546 B2	4/2012	Schuster et al.
7,388,006 B2	6/2008	Schmees et al.	8,158,613 B2	4/2012	Staniforth et al.
7,414,043 B2	8/2008	Kosemund et al.	8,158,614 B2	4/2012	Lambert et al.
7,427,413 B2	9/2008	Savoir et al.	8,163,722 B2	4/2012	Savoir et al.
7,427,609 B2	9/2008	Leonard	8,177,449 B2	5/2012	Bayly et al.
7,429,576 B2	9/2008	Labrie	8,182,833 B2	5/2012	Hermesmyer
7,431,941 B2	10/2008	Besins et al.	8,187,615 B2	5/2012	Friedman
7,456,159 B2	11/2008	Houze et al.	8,195,403 B2	6/2012	Ishikawa et al.
7,459,445 B2	12/2008	Hill et al.	8,202,736 B2	6/2012	Mousa et al.
7,465,587 B2	12/2008	Imrich	8,217,024 B2	7/2012	Ahmed et al.
7,470,433 B2	12/2008	Carrara et al.	8,221,785 B2	7/2012	Chien
7,485,666 B2	2/2009	Villanueva et al.	8,222,008 B2	7/2012	Thoene
7,497,855 B2	3/2009	Ausiello et al.	8,222,237 B2	7/2012	Nickisch et al.
7,498,303 B2	3/2009	Arnold et al.	8,227,454 B2	7/2012	Hill et al.
7,534,765 B2	5/2009	Gregg et al.	8,227,509 B2	7/2012	Castro et al.
7,534,780 B2	5/2009	Wyrwa et al.	8,241,664 B2	8/2012	Dudley et al.
7,550,142 B2	6/2009	Giles-Komar et al.	8,247,393 B2	8/2012	Ahmed et al.
7,563,565 B1	7/2009	Matsuo et al.	8,257,724 B2	9/2012	Cromack et al.
7,569,274 B2	8/2009	Besse et al.	8,257,725 B2	9/2012	Cromack et al.
7,572,779 B2	8/2009	Aloba et al.	8,268,352 B2	9/2012	Vaya et al.
7,572,780 B2	8/2009	Hermesmyer	8,268,806 B2	9/2012	Labrie
7,589,082 B2	9/2009	Savoir et al.	8,268,878 B2	9/2012	Armer et al.
7,671,027 B2	3/2010	Loumaye	8,273,730 B2	9/2012	Fernandez et al.
7,674,783 B2	3/2010	Hermesmyer	8,287,888 B2	10/2012	Song et al.
7,687,281 B2	3/2010	Roth et al.	8,288,366 B2	10/2012	Chochinov et al.
7,687,485 B2	3/2010	Levinson et al.	8,318,898 B2	11/2012	Fasel et al.
7,694,683 B2	4/2010	Callister et al.	8,324,193 B2	12/2012	Lee-Sepsick et al.
7,704,983 B1	4/2010	Hodgen et al.	8,329,680 B2	12/2012	Evans et al.
7,727,720 B2	6/2010	Dhallan	8,337,814 B2	12/2012	Osbacken et al.
7,732,408 B2	6/2010	Josephson et al.	8,344,007 B2	1/2013	Tang et al.
7,749,989 B2	7/2010	Hill et al.	8,349,820 B2	1/2013	Zeun et al.
7,767,656 B2	8/2010	Shoichet et al.	8,353,863 B2	1/2013	Imran
7,799,769 B2	9/2010	White et al.	8,357,723 B2	1/2013	Satyam
7,815,936 B2	10/2010	Hasenzahl et al.	8,361,995 B2	1/2013	Schramm
7,815,949 B2	10/2010	Cohen	8,362,091 B2	1/2013	Tamarkin et al.
7,829,115 B2	11/2010	Besins et al.	8,372,424 B2	2/2013	Berry et al.
7,829,116 B2	11/2010	Griswold et al.	8,372,806 B2	2/2013	Boehler et al.
RE42,012 E	12/2010	Deaver et al.	8,377,482 B2	2/2013	Laurie et al.
7,850,992 B2	12/2010	Kim et al.	8,377,994 B2	2/2013	Gray et al.
7,854,753 B2	12/2010	Kraft et al.	8,394,759 B2	3/2013	Barathur et al.
7,858,607 B2	12/2010	Mamchur	8,415,332 B2	4/2013	Diliberti et al.
RE42,072 E	1/2011	Deaver et al.	8,420,111 B2	4/2013	Hermesmyer
			8,435,561 B2	5/2013	Besins et al.
			8,435,972 B2	5/2013	Stein et al.
			8,449,879 B2	5/2013	Laurent-Applegate et al.
			8,450,108 B2	5/2013	Boyce



## US 8,987,237 B2

Page 5

(56)	<b>References Cited</b>					
	U.S. PATENT DOCUMENTS					
8,454,945	B2	6/2013	McCook et al.	2002/0169205	A1	11/2002 Chwalisz et al.
8,455,468	B2	6/2013	Hoffman et al.	2002/0173510	A1	11/2002 Levinson et al.
8,461,138	B2	6/2013	Boissonneault	2002/0193356	A1	12/2002 Van Beek et al.
8,476,252	B2	7/2013	Achleitner et al.	2002/0193758	A1	12/2002 Sandberg
8,481,488	B2	7/2013	Carter	2002/0197286	A1	12/2002 Brandman et al.
8,486,374	B2	7/2013	Tamarkin et al.	2003/0003139	A1	1/2003 Lipp et al.
8,486,442	B2	7/2013	Matsushita et al.	2003/0004145	A1	1/2003 Leonard
8,492,368	B2	7/2013	Vanlandingham et al.	2003/0007994	A1	1/2003 Bunt et al.
8,507,467	B2	8/2013	Matsui et al.	2003/0027772	A1	2/2003 Breton
8,512,693	B2	8/2013	Capito et al.	2003/0044453	A1	3/2003 Dittgen et al.
8,512,754	B2	8/2013	Needham	2003/0049307	A1	3/2003 Gyurik
8,518,376	B2	8/2013	Tamarkin et al.	2003/0064097	A1	4/2003 Patel et al.
8,536,159	B2	9/2013	Li et al.	2003/0072760	A1	4/2003 Sirbasku
8,540,967	B2	9/2013	Barrett et al.	2003/0073248	A1	4/2003 Roth et al.
8,541,400	B2	9/2013	Johnsson et al.	2003/0073673	A1	4/2003 Hesch
8,551,462	B2	10/2013	Goldstein et al.	2003/0077297	A1 *	4/2003 Chen et al. .... 424/400
8,557,281	B2	10/2013	Halliday et al.	2003/0078245	A1	4/2003 Bennink et al.
8,568,374	B2	10/2013	De Graaff et al.	2003/0091620	A1	5/2003 Fikstad et al.
8,591,951	B2	11/2013	Kohn et al.	2003/0091640	A1	5/2003 Ramanathan et al.
8,613,951	B2	12/2013	Zale et al.	2003/0092691	A1	5/2003 Besse et al.
8,633,178	B2	1/2014	Bernick et al.	2003/0096012	A1	5/2003 Besse et al.
8,633,180	B2	1/2014	Li et al.	2003/0104048	A1	6/2003 Patel et al.
8,636,787	B2	1/2014	Sabaria	2003/0109507	A1	6/2003 Franke et al.
8,636,982	B2	1/2014	Tamarkin et al.	2003/0113268	A1	6/2003 Buenafae et al.
8,653,129	B2	2/2014	Fein et al.	2003/0114420	A1	6/2003 Salvati et al.
8,658,627	B2	2/2014	Voskuhl	2003/0114430	A1	6/2003 MacLeod et al.
8,658,628	B2	2/2014	Baucom	2003/0124182	A1	7/2003 Shojaei et al.
8,663,681	B2	3/2014	Ahmed et al.	2003/0124191	A1	7/2003 Besse et al.
8,663,692	B1	3/2014	Mueller et al.	2003/0130558	A1	7/2003 Massara et al.
8,663,703	B2	3/2014	Lerner et al.	2003/0144258	A1	7/2003 Heil et al.
8,664,207	B2	3/2014	Li et al.	2003/0157157	A1	8/2003 Luo et al.
8,669,293	B2	3/2014	Levy et al.	2003/0166509	A1	9/2003 Edwards et al.
8,679,552	B2	3/2014	Guthery	2003/0170295	A1	9/2003 Kim et al.
8,697,127	B2	4/2014	Sah	2003/0175329	A1	9/2003 Azarnoff et al.
8,697,710	B2	4/2014	Li et al.	2003/0175333	A1	9/2003 Shefer et al.
8,703,105	B2	4/2014	Tamarkin et al.	2003/0180352	A1	9/2003 Patel et al.
8,709,385	B2	4/2014	Tamarkin et al.	2003/0181353	A1	9/2003 Nyce
8,709,451	B2	4/2014	Nam et al.	2003/0181728	A1	9/2003 Salvati et al.
8,715,735	B2	5/2014	Funke et al.	2003/0191096	A1	10/2003 Leonard et al.
8,721,331	B2	5/2014	Raghuprasad	2003/0195177	A1	10/2003 Leonard et al.
8,722,021	B2	5/2014	Friedman et al.	2003/0215496	A1	11/2003 Patel et al.
8,734,846	B2	5/2014	Ali et al.	2003/0219402	A1	11/2003 Rutter
8,735,381	B2	5/2014	Podolski	2003/0220297	A1	11/2003 Bernstein et al.
8,741,336	B2	6/2014	Dipierro et al.	2003/0224057	A1	12/2003 Martin-Letellier et al.
8,741,373	B2	6/2014	Bromley et al.	2003/0224059	A1	12/2003 Lerner et al.
8,753,661	B2	6/2014	Steinmuller-Nethl et al.	2003/0225047	A1	12/2003 Caubel et al.
8,784,882	B2	7/2014	Mattern	2003/0225048	A1	12/2003 Caubel et al.
2001/0005728	A1	6/2001	Guittard et al.	2003/0225050	A1	12/2003 Grawe et al.
2001/0009673	A1	7/2001	Lipp et al.	2003/0228686	A1	12/2003 Klausner et al.
2001/0021816	A1	9/2001	Caillouette	2003/0229057	A1	12/2003 Caubel et al.
2001/0023261	A1	9/2001	Ryoo et al.	2003/0235596	A1	12/2003 Gao et al.
2001/0027189	A1	10/2001	Bennink et al.	2003/0236236	A1 *	12/2003 Chen et al. .... 514/171
2001/0029357	A1	10/2001	Bunt et al.	2004/0009960	A1	1/2004 Heil et al.
2001/0031747	A1	10/2001	Deziegler et al.	2004/0022820	A1	2/2004 Anderson
2001/0034340	A1	10/2001	Pickar	2004/0034001	A1	2/2004 Karara
2001/0053383	A1	12/2001	Miranda et al.	2004/0037881	A1	2/2004 Guittard et al.
2001/0056068	A1	12/2001	Chwalisz et al.	2004/0039356	A1	2/2004 Maki et al.
2002/0012710	A1	1/2002	Lansky	2004/0043043	A1	3/2004 Schlyter et al.
2002/0026158	A1	2/2002	Rathbone et al.	2004/0043943	A1	3/2004 Guittard et al.
2002/0028788	A1	3/2002	Bunt et al.	2004/0044080	A1	3/2004 Place et al.
2002/0035070	A1	3/2002	Gardlik et al.	2004/0048900	A1	3/2004 Flood
2002/0058648	A1	5/2002	Hammerly	2004/0052824	A1	3/2004 Chacra-Vernet et al.
2002/0058926	A1	5/2002	Rathbone et al.	2004/0073024	A1	4/2004 Metcalf, III et al.
2002/0076441	A1	6/2002	Shih et al.	2004/0077605	A1	4/2004 Salvati et al.
2002/0102308	A1	8/2002	Wei et al.	2004/0077606	A1	4/2004 Salvati et al.
2002/0107230	A1	8/2002	Waldon et al.	2004/0087548	A1	5/2004 Salvati et al.
2002/0114803	A1	8/2002	Deaver et al.	2004/0087564	A1	5/2004 Wright et al.
2002/0119174	A1	8/2002	Gardlik et al.	2004/0089308	A1	5/2004 Welch
2002/0119198	A1	8/2002	Gao et al.	2004/0092494	A9	5/2004 Dudley
2002/0132801	A1	9/2002	Heil et al.	2004/0092583	A1	5/2004 Shanahan-Prendergast
2002/0137749	A1	9/2002	Levinson et al.	2004/0097468	A1	5/2004 Wimalawansa
2002/0142017	A1	10/2002	Simonnet et al.	2004/0101557	A1	5/2004 Gibson et al.
2002/0151530	A1	10/2002	Leonard et al.	2004/0106542	A1	6/2004 Deaver et al.
2002/0156394	A1	10/2002	Mehrotra et al.	2004/0110732	A1	6/2004 Masini-Etevel et al.
2002/0169150	A1	11/2002	Pickar	2004/0131670	A1	7/2004 Gao
				2004/0138103	A1	7/2004 Patt
				2004/0142012	A1	7/2004 Bunt et al.
				2004/0146539	A1	7/2004 Gupta
				2004/0146894	A1	7/2004 Warrington et al.

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

2004/0161435	A1	8/2004	Gupta	2006/0069031	A1	3/2006	Loumaye
2004/0176324	A1	9/2004	Salvati et al.	2006/0078618	A1	4/2006	Constantinides et al.
2004/0176336	A1	9/2004	Rodriguez	2006/0083778	A1	4/2006	Allison et al.
2004/0185104	A1	9/2004	Piao et al.	2006/0084704	A1	4/2006	Shih et al.
2004/0191207	A1	9/2004	Lipari et al.	2006/0088580	A1	4/2006	Meconi et al.
2004/0191276	A1	9/2004	Muni	2006/0089337	A1	4/2006	Casper et al.
2004/0198706	A1	10/2004	Carrara	2006/0093678	A1	5/2006	Chickering, III et al.
2004/0210280	A1	10/2004	Liedtke	2006/0100180	A1	5/2006	Nubbemeyer et al.
2004/0213744	A1	10/2004	Lulla et al.	2006/0106004	A1	5/2006	Brody et al.
2004/0219124	A1	11/2004	Gupta	2006/0110415	A1	5/2006	Gupta
2004/0225140	A1	11/2004	Fernandez et al.	2006/0111424	A1	5/2006	Salvati et al.
2004/0234606	A1	11/2004	Levine et al.	2006/0121102	A1	6/2006	Chiang
2004/0241219	A1	12/2004	Hille et al.	2006/0121626	A1	6/2006	Imrich
2004/0253319	A1	12/2004	Netke et al.	2006/0134188	A1	6/2006	Podhaisky et al.
2004/0259817	A1	12/2004	Waldon et al.	2006/0135619	A1	6/2006	Kick et al.
2004/0266745	A1	12/2004	Schwanitz et al.	2006/0165744	A1	7/2006	Jamil et al.
2005/0003003	A1	1/2005	Basu et al.	2006/0193789	A1	8/2006	Tamarkin et al.
2005/0004088	A1	1/2005	Hesch	2006/0194775	A1	8/2006	Tofovic et al.
2005/0009800	A1	1/2005	Thumbeck et al.	2006/0204557	A1	9/2006	Gupta et al.
2005/0014729	A1	1/2005	Pulaski	2006/0233743	A1	10/2006	Kelly
2005/0020550	A1	1/2005	Morris et al.	2006/0233841	A1	10/2006	Brodbeck et al.
2005/0020552	A1	1/2005	Aschkenasay et al.	2006/0235037	A1	10/2006	Purandare et al.
2005/0021009	A1	1/2005	Massara et al.	2006/0240111	A1	10/2006	Fernandez et al.
2005/0025833	A1	2/2005	Aschkenasay et al.	2006/0246122	A1	11/2006	Langguth et al.
2005/0031651	A1	2/2005	Gervais et al.	2006/0247216	A1	11/2006	Haj-Yehia
2005/0042173	A1	2/2005	Besse et al.	2006/0247221	A1	11/2006	Coelingh et al.
2005/0042268	A1	2/2005	Aschkenasay et al.	2006/0251581	A1	11/2006	McIntyre et al.
2005/0048116	A1	3/2005	Straub et al.	2006/0252049	A1	11/2006	Shuler et al.
2005/0054991	A1	3/2005	Tobyn et al.	2006/0257472	A1	11/2006	Neilsen
2005/0079138	A1	4/2005	Chickering, III et al.	2006/0275218	A1	12/2006	Tamarkin et al.
2005/0085453	A1	4/2005	Govindarajan	2006/0275360	A1	12/2006	Ahmed et al.
2005/0101579	A1	5/2005	Shippen	2006/0276414	A1	12/2006	Coelingh et al.
2005/0113350	A1	5/2005	Duesterberg et al.	2006/0280771	A1	12/2006	Groenewegen et al.
2005/0118244	A1	6/2005	Theobald et al.	2006/0280797	A1	12/2006	Shoichet et al.
2005/0118272	A1	6/2005	Besse et al.	2006/0280800	A1	12/2006	Nagi et al.
2005/0129756	A1	6/2005	Podhaisky et al.	2006/0292223	A1	12/2006	Woolfson et al.
2005/0152956	A1	7/2005	Dudley	2007/0004693	A1	1/2007	Woolfson et al.
2005/0153946	A1	7/2005	Hirsh et al.	2007/0004694	A1	1/2007	Woolfson et al.
2005/0164977	A1	7/2005	Coelingh Bennink	2007/0009559	A1	1/2007	Li et al.
2005/0182105	A1	8/2005	Nirschl et al.	2007/0009594	A1	1/2007	Grubb et al.
2005/0186141	A1	8/2005	Gonda et al.	2007/0010550	A1	1/2007	McKenzie
2005/0187267	A1	8/2005	Hamann et al.	2007/0014839	A1	1/2007	Bracht
2005/0192253	A1	9/2005	Salvati et al.	2007/0015698	A1	1/2007	Kleinman et al.
2005/0192310	A1	9/2005	Gavai et al.	2007/0021360	A1	1/2007	Nyce et al.
2005/0196434	A1	9/2005	Brierre	2007/0027201	A1	2/2007	McComas et al.
2005/0207990	A1	9/2005	Funke et al.	2007/0031491	A1	2/2007	Levine et al.
2005/0214384	A1	9/2005	Juturu et al.	2007/0037780	A1	2/2007	Ebert et al.
2005/0220825	A1	10/2005	Funke et al.	2007/0037782	A1	2/2007	Hibino et al.
2005/0220900	A1	10/2005	Popp et al.	2007/0042038	A1	2/2007	Besse
2005/0222106	A1	10/2005	Bracht	2007/0060589	A1	3/2007	Purandare et al.
2005/0239747	A1	10/2005	Yang et al.	2007/0066628	A1	3/2007	Zhang et al.
2005/0239758	A1	10/2005	Roby	2007/0066637	A1	3/2007	Zhang et al.
2005/0244360	A1	11/2005	Billoni	2007/0066675	A1	3/2007	Zhang et al.
2005/0244522	A1	11/2005	Carrara et al.	2007/0078091	A1	4/2007	Hubler et al.
2005/0245902	A1	11/2005	Cornish et al.	2007/0088029	A1	4/2007	Balog et al.
2005/0250746	A1	11/2005	Iammatteo	2007/0093548	A1	4/2007	Diffendal et al.
2005/0250750	A1	11/2005	Cummings et al.	2007/0116729	A1	5/2007	Palepu
2005/0250753	A1	11/2005	Fink et al.	2007/0116829	A1	5/2007	Prakash et al.
2005/0256028	A1	11/2005	Yun et al.	2007/0128263	A1	6/2007	Gargiulo et al.
2005/0266078	A1	12/2005	Jorda et al.	2007/0154533	A1	7/2007	Dudley
2005/0266088	A1	12/2005	Hinrichs et al.	2007/0167418	A1	7/2007	Ferguson
2005/0271597	A1	12/2005	Keith	2007/0178166	A1	8/2007	Bernstein et al.
2005/0271598	A1	12/2005	Frieman et al.	2007/0184558	A1	8/2007	Roth et al.
2005/0272685	A1	12/2005	Hung	2007/0185068	A1	8/2007	Ferguson et al.
2005/0272712	A1	12/2005	Grubb et al.	2007/0190022	A1	8/2007	Bacopoulos et al.
2006/0009428	A1	1/2006	Grubb et al.	2007/0191319	A1	8/2007	Ke et al.
2006/0014728	A1	1/2006	Chwalisz et al.	2007/0196415	A1	8/2007	Chen et al.
2006/0018937	A1	1/2006	Friedman et al.	2007/0196433	A1	8/2007	Ron et al.
2006/0019978	A1	1/2006	Balog	2007/0207225	A1	9/2007	Squadrito
2006/0020002	A1	1/2006	Salvati et al.	2007/0225281	A1	9/2007	Zhang et al.
2006/0030615	A1	2/2006	Fensome et al.	2007/0232574	A1	10/2007	Galey et al.
2006/0034889	A1	2/2006	Jo et al.	2007/0238713	A1	10/2007	Gast et al.
2006/0034904	A1	2/2006	Weimann	2007/0243229	A1	10/2007	Smith et al.
2006/0051391	A1	3/2006	Dvoskin et al.	2007/0248658	A1	10/2007	Zurdo et al.
2006/0052341	A1	3/2006	Cornish et al.	2007/0254858	A1	11/2007	Cronk
				2007/0255197	A1	11/2007	Humberstone et al.
				2007/0264309	A1	11/2007	Chollet et al.
				2007/0264345	A1	11/2007	Eros et al.
				2007/0264349	A1	11/2007	Lee et al.



## US 8,987,237 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

2007/0286819	A1	12/2007	Devries et al.	2009/0175799	A1	7/2009	Tamarkin et al.
2007/0287688	A1	12/2007	Chan et al.	2009/0181088	A1	7/2009	Song et al.
2007/0287789	A1	12/2007	Jones et al.	2009/0186081	A1	7/2009	Holm et al.
2007/0292359	A1	12/2007	Friedman et al.	2009/0197843	A1	8/2009	Notelovitz et al.
2007/0292387	A1	12/2007	Jon et al.	2009/0203658	A1	8/2009	Marx et al.
2007/0292461	A1	12/2007	Tamarkin et al.	2009/0214474	A1	8/2009	Jennings
2007/0292493	A1	12/2007	Brierre	2009/0227025	A1	9/2009	Nichols et al.
2007/0298089	A1	12/2007	Saeki et al.	2009/0227550	A1	9/2009	Mattern
2008/0026035	A1	1/2008	Chollet et al.	2009/0232897	A1	9/2009	Sahoo et al.
2008/0026040	A1	1/2008	Farr et al.	2009/0258096	A1	10/2009	Cohen
2008/0038219	A1	2/2008	Mosbaugh et al.	2009/0264395	A1	10/2009	Creasy et al.
2008/0038350	A1	2/2008	Gerecke et al.	2009/0269403	A1	10/2009	Shaked et al.
2008/0039405	A1	2/2008	Langley et al.	2009/0285772	A1	11/2009	Phiasivongsa et al.
2008/0050317	A1	2/2008	Tamarkin et al.	2009/0285869	A1	11/2009	Trimble
2008/0051351	A1	2/2008	Ghisalberti	2009/0318558	A1	12/2009	Kim et al.
2008/0063607	A1	3/2008	Tamarkin et al.	2009/0324714	A1	12/2009	Liu et al.
2008/0069779	A1	3/2008	Tamarkin et al.	2009/0325916	A1	12/2009	Zhang et al.
2008/0069791	A1	3/2008	Beissert	2010/0008985	A1	1/2010	Pellikaan et al.
2008/0085877	A1	4/2008	Bortz	2010/0028360	A1	2/2010	Atwood
2008/0095831	A1	4/2008	Mc Graw	2010/0034838	A1	2/2010	Staniforth et al.
2008/0095838	A1	4/2008	Abou Chacra-Vernet	2010/0034880	A1	2/2010	Sintov et al.
2008/0113953	A1	5/2008	Devries et al.	2010/0040671	A1	2/2010	Ahmed et al.
2008/0114050	A1	5/2008	Fensome et al.	2010/0048523	A1	2/2010	Bachman et al.
2008/0119537	A1	5/2008	Zhang et al.	2010/0055138	A1	3/2010	Margulies et al.
2008/0125402	A1	5/2008	Diliberti et al.	2010/0074959	A1	3/2010	Hansom et al.
2008/0138379	A1	6/2008	Jennings-Spring	2010/0086501	A1	4/2010	Chang et al.
2008/0138390	A1	6/2008	Hsu et al.	2010/0086599	A1	4/2010	Huempel et al.
2008/0139392	A1	6/2008	Acosta-Zara et al.	2010/0092568	A1	4/2010	Lerner et al.
2008/0145423	A1	6/2008	Khan et al.	2010/0105071	A1	4/2010	Laufer et al.
2008/0153789	A1	6/2008	Dmowski et al.	2010/0119585	A1	5/2010	Hille et al.
2008/0175814	A1	7/2008	Phiasivongsa et al.	2010/0129320	A1	5/2010	Phiasivongsa et al.
2008/0175905	A1	7/2008	Liu et al.	2010/0136105	A1	6/2010	Chen et al.
2008/0175908	A1	7/2008	Liu et al.	2010/0137265	A1	6/2010	Leonard
2008/0188829	A1	8/2008	Creasy	2010/0137271	A1	6/2010	Chen et al.
2008/0206156	A1	8/2008	Cronk	2010/0143420	A1	6/2010	Shenoy et al.
2008/0206159	A1	8/2008	Tamarkin et al.	2010/0143481	A1	6/2010	Shenoy et al.
2008/0206161	A1	8/2008	Tamarkin et al.	2010/0150993	A1	6/2010	Theobald et al.
2008/0214512	A1	9/2008	Seitz et al.	2010/0152144	A1	6/2010	Hermesmyer
2008/0220069	A1	9/2008	Allison	2010/0168228	A1	7/2010	Bose et al.
2008/0226698	A1	9/2008	Tang et al.	2010/0183723	A1	7/2010	Laurent-Applegate
2008/0227763	A1	9/2008	Lanquetin et al.	2010/0184736	A1	7/2010	Coelingh Bennink et al.
2008/0234199	A1	9/2008	Katamreddym et al.	2010/0190758	A1	7/2010	Fausser et al.
2008/0234240	A1	9/2008	Duesterberg et al.	2010/0204326	A1	8/2010	D Souza
2008/0255078	A1	10/2008	Katamreddym et al.	2010/0210994	A1	8/2010	Zarif
2008/0255089	A1	10/2008	Katamreddym et al.	2010/0221195	A1	9/2010	Tamarkin et al.
2008/0261931	A1	10/2008	Hedner et al.	2010/0227797	A1	9/2010	Axelsson et al.
2008/0299220	A1	12/2008	Tamarkin et al.	2010/0240626	A1	9/2010	Kulkarni et al.
2008/0306036	A1	12/2008	Katamreddym et al.	2010/0247482	A1	9/2010	Cui et al.
2008/0312197	A1	12/2008	Rodriguez	2010/0247632	A1	9/2010	Dong et al.
2008/0312198	A1	12/2008	Rodriguez	2010/0247635	A1	9/2010	Rosenberg et al.
2008/0319078	A1	12/2008	Katamreddym et al.	2010/0255085	A1	10/2010	Liu et al.
2009/0004246	A1	1/2009	Woolfson et al.	2010/0273730	A1	10/2010	Hsu et al.
2009/0010968	A1	1/2009	Allart et al.	2010/0278759	A1	11/2010	Murad
2009/0011041	A1	1/2009	Musaeva et al.	2010/0279988	A1	11/2010	Setiawan et al.
2009/0017120	A1	1/2009	Trimble et al.	2010/0291191	A1	11/2010	Shoichet et al.
2009/0022683	A1	1/2009	Song et al.	2010/0292199	A1	11/2010	Leverd et al.
2009/0047357	A1	2/2009	Tomohira et al.	2010/0303825	A9	12/2010	Sirbasku
2009/0053294	A1	2/2009	Prendergast	2010/0312137	A1	12/2010	Gilmour et al.
2009/0060982	A1	3/2009	Ron et al.	2010/0316724	A1	12/2010	Whitfield et al.
2009/0060997	A1	3/2009	Seitz et al.	2010/0322884	A1	12/2010	Dipietro et al.
2009/0068118	A1	3/2009	Eini et al.	2010/0330168	A1	12/2010	Gicquel et al.
2009/0081206	A1	3/2009	Leibovitz	2011/0028439	A1	2/2011	Witt-Enderby et al.
2009/0081278	A1	3/2009	De Graaff et al.	2011/0039814	A1	2/2011	Huatan et al.
2009/0081303	A1	3/2009	Savoir et al.	2011/0053845	A1	3/2011	Levine et al.
2009/0092656	A1	4/2009	Klamerus et al.	2011/0076775	A1	3/2011	Stewart et al.
2009/0093440	A1	4/2009	Murad	2011/0076776	A1	3/2011	Stewart et al.
2009/0098069	A1	4/2009	Vacca	2011/0086825	A1	4/2011	Chatroux
2009/0099106	A1	4/2009	Phiasivongsa et al.	2011/0087192	A1	4/2011	Uhland et al.
2009/0099149	A1	4/2009	Liu et al.	2011/0091555	A1	4/2011	De Luigi Bruschi et al.
2009/0130029	A1	5/2009	Tamarkin et al.	2011/0098258	A1	4/2011	Masini-Eteve et al.
2009/0131385	A1	5/2009	Voskuhl	2011/0098631	A1	4/2011	McIntyre et al.
2009/0137478	A1	5/2009	Bernstein et al.	2011/0104268	A1	5/2011	Pachot et al.
2009/0137538	A1	5/2009	Klamerus et al.	2011/0104289	A1	5/2011	Savoir Vilboeuf et al.
2009/0143344	A1	6/2009	Chang	2011/0130372	A1	6/2011	Agostinacchio et al.
				2011/0135719	A1	6/2011	Besins et al.
				2011/0142945	A1	6/2011	Chen et al.
				2011/0152840	A1	6/2011	Lee et al.
				2011/0158920	A1	6/2011	Morley et al.
				2011/0171140	A1	7/2011	Illum et al.

## US 8,987,237 B2

Page 8

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2011/0182997	A1	7/2011	Lewis et al.	2012/0316496	A1	12/2012	Hoffmann et al.
2011/0190201	A1	8/2011	Hyde et al.	2012/0321579	A1	12/2012	Edelson et al.
2011/0195031	A1	8/2011	Du	2012/0322779	A9	12/2012	Voskuhl
2011/0195114	A1	8/2011	Carrara et al.	2012/0328549	A1	12/2012	Edelson et al.
2011/0195944	A1	8/2011	Mura et al.	2012/0329738	A1	12/2012	Liu
2011/0217341	A1	9/2011	Sah	2013/0004619	A1	1/2013	Chow et al.
2011/0238003	A1	9/2011	Bruno-Raimondi et al.	2013/0011342	A1	1/2013	Tamarkin et al.
2011/0244043	A1	10/2011	Xu et al.	2013/0017239	A1	1/2013	Viladot et al.
2011/0250256	A1	10/2011	Hyun-Oh et al.	2013/0022674	A1	1/2013	Dudley et al.
2011/0250259	A1	10/2011	Buckman	2013/0023505	A1	1/2013	Garfield et al.
2011/0250274	A1	10/2011	Shaked et al.	2013/0023823	A1	1/2013	Simpson et al.
2011/0256092	A1	10/2011	Phiasivongsa et al.	2013/0028850	A1	1/2013	Tamarkin et al.
2011/0262373	A1	10/2011	Umbert	2013/0029947	A1	1/2013	Nachaeagari et al.
2011/0262494	A1	10/2011	Achleitner et al.	2013/0029957	A1	1/2013	Giliyar et al.
2011/0268665	A1	11/2011	Tamarkin et al.	2013/0045266	A1	2/2013	Choi et al.
2011/0275584	A1	11/2011	Wilckens et al.	2013/0045953	A1	2/2013	Sitruk-Ware et al.
2011/0281832	A1	11/2011	Li et al.	2013/0059795	A1	3/2013	Lo et al.
2011/0287094	A1	11/2011	Penhasi et al.	2013/0064897	A1	3/2013	Binay
2011/0293720	A1	12/2011	General et al.	2013/0072466	A1	3/2013	Choi et al.
2011/0294738	A1	12/2011	Ren et al.	2013/0084257	A1	4/2013	Ishida et al.
2011/0300167	A1	12/2011	McMurry et al.	2013/0085123	A1	4/2013	Li et al.
2011/0301087	A1	12/2011	McBride et al.	2013/0089574	A1	4/2013	Schmidt-Gollwitzer et al.
2011/0306579	A1	12/2011	Stein	2013/0090318	A1	4/2013	Ulmann et al.
2011/0311592	A1	12/2011	Birbara	2013/0102781	A1	4/2013	Bevill et al.
2011/0312927	A1	12/2011	Nachaeagari et al.	2013/0108551	A1	5/2013	Langereis et al.
2011/0312928	A1	12/2011	Nachaeagari et al.	2013/0116215	A1	5/2013	Coma et al.
2011/0318405	A1	12/2011	Erwin	2013/0116222	A1	5/2013	Arnold et al.
2011/0318431	A1	12/2011	Gulati	2013/0122051	A1	5/2013	Abidi et al.
2012/0009276	A1	1/2012	De Groote	2013/0123175	A1	5/2013	Hill et al.
2012/0015350	A1	1/2012	Nabatiyan et al.	2013/0123220	A1	5/2013	Queiroz
2012/0021041	A1	1/2012	Rossi et al.	2013/0123351	A1	5/2013	Dewitt
2012/0028888	A1	2/2012	Janz et al.	2013/0129818	A1	5/2013	Bernick et al.
2012/0028910	A1	2/2012	Combal et al.	2013/0131027	A1	5/2013	Pakkalin et al.
2012/0028936	A1	2/2012	Gloger et al.	2013/0131028	A1	5/2013	Snyder et al.
2012/0045532	A1	2/2012	Cohen	2013/0131029	A1	5/2013	Bakker et al.
2012/0046264	A1	2/2012	Simes et al.	2013/0149314	A1	6/2013	Bullerdiek et al.
2012/0046518	A1	2/2012	Yoakum et al.	2013/0164225	A1	6/2013	Tamarkin et al.
2012/0052077	A1	3/2012	Truitt et al.	2013/0164346	A1	6/2013	Lee et al.
2012/0058171	A1	3/2012	De Graaff et al.	2013/0165744	A1	6/2013	Carson et al.
2012/0058962	A1	3/2012	Cumming et al.	2013/0178452	A1	7/2013	King
2012/0058979	A1	3/2012	Keith et al.	2013/0183254	A1	7/2013	Zhou
2012/0064135	A1	3/2012	Levin et al.	2013/0183325	A1	7/2013	Bottoni et al.
2012/0065179	A1	3/2012	Andersson	2013/0189193	A1	7/2013	Tamarkin et al.
2012/0087872	A1	4/2012	Tamarkin et al.	2013/0189196	A1	7/2013	Tamarkin et al.
2012/0101073	A1	4/2012	Mannion et al.	2013/0189230	A1	7/2013	Shoichet et al.
2012/0121517	A1	5/2012	Song et al.	2013/0189368	A1	7/2013	Mosqueira et al.
2012/0121692	A1	5/2012	Xu et al.	2013/0210709	A1	8/2013	McMurry et al.
2012/0122829	A1	5/2012	Taravella et al.	2013/0216550	A1	8/2013	Penninger et al.
2012/0128625	A1	5/2012	Shalwitz et al.	2013/0216596	A1	8/2013	Viladot Petit et al.
2012/0128654	A1	5/2012	Terpstra et al.	2013/0224177	A1	8/2013	Kim et al.
2012/0128683	A1	5/2012	Shantha	2013/0224257	A1	8/2013	Sah et al.
2012/0128733	A1	5/2012	Perrin et al.	2013/0224268	A1	8/2013	Alam et al.
2012/0128777	A1	5/2012	Keck et al.	2013/0224300	A1	8/2013	Maggio
2012/0129773	A1	5/2012	Geier et al.	2013/0225412	A1	8/2013	Sardari Lodriche et al.
2012/0129819	A1	5/2012	Vancaillie et al.	2013/0225542	A1	8/2013	Poegh et al.
2012/0136013	A1	5/2012	Li et al.	2013/0226113	A1	8/2013	Schumacher et al.
2012/0142645	A1	6/2012	Marx	2013/0243696	A1	9/2013	Wang et al.
2012/0148670	A1	6/2012	Kim et al.	2013/0245253	A1	9/2013	Marx et al.
2012/0149748	A1	6/2012	Shanler et al.	2013/0245570	A1	9/2013	Jackson
2012/0172343	A1	7/2012	Lindenthal et al.	2013/0261096	A1	10/2013	Merian et al.
2012/0184515	A1	7/2012	Klar et al.	2013/0266645	A1	10/2013	Becker et al.
2012/0231052	A1	9/2012	Sitruk-Ware et al.	2013/0267485	A1	10/2013	Da Silva Maia Filho
2012/0232011	A1	9/2012	Kneissel et al.	2013/0273167	A1	10/2013	Lee et al.
2012/0232042	A1	9/2012	Klar et al.	2013/0274211	A1	10/2013	Burman et al.
2012/0263679	A1	10/2012	Marlow et al.	2013/0280213	A1	10/2013	Voskuhl
2012/0269721	A1	10/2012	Weng et al.	2013/0316374	A1	11/2013	Penninger et al.
2012/0269878	A2	10/2012	Cantor et al.	2013/0317065	A1	11/2013	Tatani et al.
2012/0277249	A1	11/2012	Andersson et al.	2013/0317315	A1	11/2013	Lu et al.
2012/0277727	A1	11/2012	Doshi et al.	2013/0324565	A1	12/2013	Li et al.
2012/0283671	A1	11/2012	Shibata et al.	2013/0331363	A1	12/2013	Li et al.
2012/0295911	A1	11/2012	Mannion et al.	2013/0338124	A1	12/2013	Li et al.
2012/0301517	A1	11/2012	Zhang et al.	2013/0345187	A1	12/2013	Rodriguez Oquendo
2012/0301538	A1	11/2012	Gordon-Beresford et al.	2014/0018335	A1	1/2014	Tatani et al.
2012/0302535	A1	11/2012	Caufriez et al.	2014/0024590	A1	1/2014	Weidhaas et al.
2012/0316130	A1	12/2012	Hendrix	2014/0031289	A1	1/2014	Song et al.
				2014/0031323	A1	1/2014	Perez
				2014/0066416	A1	3/2014	Leunis et al.
				2014/0072531	A1	3/2014	Kim et al.
				2014/0079686	A1	3/2014	Barman et al.

## US 8,987,237 B2

Page 9

## (56) References Cited

## U.S. PATENT DOCUMENTS

2014/0088058 A1 3/2014 Maurizio  
 2014/0088059 A1 3/2014 Perumal et al.  
 2014/0094426 A1 4/2014 Drummond et al.  
 2014/0100159 A1 4/2014 Conrad  
 2014/0100206 A1 4/2014 Bernick et al.  
 2014/0113889 A1 4/2014 Connor et al.  
 2014/0127185 A1 5/2014 Stein et al.  
 2014/0127280 A1 5/2014 Duesterberg et al.  
 2014/0127308 A1 5/2014 Opara et al.  
 2014/0128798 A1 5/2014 Janson et al.  
 2014/0186332 A1 7/2014 Ezrin et al.  
 2014/0187487 A1 7/2014 Shoichet et al.  
 2014/0193523 A1 7/2014 Henry  
 2014/0194396 A1 7/2014 Li et al.  
 2014/0206616 A1 7/2014 Ko et al.

## FOREIGN PATENT DOCUMENTS

EP 0275716 A1 7/1988  
 EP 0622075 A1 11/1994  
 EP 0785211 A1 1/1996  
 EP 0811381 A1 6/1997  
 EP 0785212 A1 7/1997  
 EP 1094781 B1 7/2008  
 EP 2191833 A1 6/2010  
 GB 1589946 A1 2/1921  
 GB 452238 A 8/1936  
 GB 720561 A 12/1954  
 GB 848881 A 9/1960  
 GB 874368 A 8/1961  
 IN 216026 A 3/2008  
 IN 2005KO00053 A 9/2009  
 IN 244217 A 11/2010  
 WO 9011064 A1 10/1990  
 WO 9317686 A1 9/1993  
 WO 9422426 A1 10/1994  
 WO 9530409 A1 11/1995  
 WO 9609826 A2 4/1996  
 WO 9619975 7/1996  
 WO 9630000 A1 10/1996  
 WO 9705491 2/1997  
 WO 9743989 A1 11/1997  
 WO 9810293 A1 3/1998  
 WO 9832465 A1 7/1998  
 WO 9851280 A1 11/1998  
 WO 9932072 7/1999  
 WO 9939700 A1 8/1999  
 WO 9942109 A1 8/1999  
 WO 9943304 9/1999  
 WO 9948477 A1 9/1999  
 WO 9953910 A2 10/1999  
 WO 9963974 A2 12/1999  
 WO 0001351 A1 1/2000  
 WO 0006175 A1 2/2000  
 WO 0038659 A1 7/2000  
 WO 0045795 A2 8/2000  
 WO 0050007 A1 8/2000  
 WO 0059577 A1 10/2000  
 WO 0076522 A1 12/2000  
 WO 0137808 A1 5/2001  
 WO 0154699 A1 8/2001  
 WO 0160325 A1 8/2001  
 WO 0207700 A2 2/2002  
 WO 0211768 A1 2/2002  
 WO 0222132 A2 3/2002  
 WO 0240008 A2 5/2002  
 WO 0241878 5/2002  
 WO 02053131 A1 7/2002  
 WO 02078602 A2 10/2002  
 WO 02078604 A2 10/2002  
 WO 03028667 4/2003  
 WO 03041718 A1 5/2003  
 WO 03041741 A1 5/2003  
 WO 03068186 A1 8/2003

WO 03077923 A1 9/2003  
 WO 03082254 A1 10/2003  
 WO 03092588 A2 11/2003  
 WO WO2004014432 2/2004  
 WO 2004017983 A1 3/2004  
 WO 2004032897 A2 4/2004  
 WO 2004052336 A2 6/2004  
 WO 2004054540 A2 7/2004  
 WO 2004080413 A2 9/2004  
 WO 2005027911 A1 3/2005  
 WO 2005030175 A1 4/2005  
 WO 2005087194 A1 9/2005  
 WO 2005087199 A2 9/2005  
 WO WO2005081825 9/2005  
 WO 2005105059 A1 11/2005  
 WO 2005115335 A1 12/2005  
 WO 2005120470 A1 12/2005  
 WO 2005120517 A1 12/2005  
 WO 2006013369 A2 2/2006  
 WO 2006034090 A1 3/2006  
 WO 2006036899 A2 4/2006  
 WO 2006053172 A2 5/2006  
 WO 2006105615 A1 10/2006  
 WO 2006113505 A2 10/2006  
 WO 2006138686 A1 12/2006  
 WO 2006138735 A2 12/2006  
 WO 2007045027 A1 4/2007  
 WO 2007103294 A2 9/2007  
 WO WO2007120868 10/2007  
 WO 2007123790 A1 11/2007  
 WO 2007124250 A2 11/2007  
 WO 2007144151 A1 12/2007  
 WO 2008049516 A3 5/2008  
 WO 2008152444 A2 12/2008  
 WO 2009002542 A1 12/2008  
 WO 2009036311 A1 3/2009  
 WO 2009040818 4/2009  
 WO 2009069006 A2 6/2009  
 WO 2009098072 A2 8/2009  
 WO 2009133352 A2 11/2009  
 WO 2010033188 A2 3/2010  
 WO WO2010146872 12/2010  
 WO 2011000210 A1 1/2011  
 WO 2011073995 A2 6/2011  
 WO 2011120084 A1 10/2011  
 WO 2011128336 A1 10/2011  
 WO 2012009778 A2 1/2012  
 WO 2012024361 A1 2/2012  
 WO WO2012055814 A1 5/2012  
 WO WO2012055840 A1 5/2012  
 WO WO2012065740 5/2012  
 WO WO2012098090 A1 7/2012  
 WO WO2012116277 A1 8/2012  
 WO WO2012118563 A2 9/2012  
 WO WO2012120365 A1 9/2012  
 WO WO2012127501 A2 9/2012  
 WO WO2012156561 A1 11/2012  
 WO WO2012156822 A1 11/2012  
 WO WO2012158483 A2 11/2012  
 WO WO2012166909 A1 12/2012  
 WO WO2012170578 A1 12/2012  
 WO WO2013011501 A1 1/2013  
 WO WO2013025449 A1 2/2013  
 WO WO2013028639 A1 2/2013  
 WO WO2013035101 A1 3/2013  
 WO WO2013044067 A1 3/2013  
 WO WO2013045404 A2 4/2013  
 WO WO2013059285 A1 4/2013  
 WO WO2013063279 A1 5/2013  
 WO WO2013064620 A1 5/2013  
 WO WO2013071281 A1 5/2013  
 WO WO2013088254 6/2013  
 WO WO2013102665 A1 7/2013  
 WO WO2013106437 A1 7/2013  
 WO WO2013113690 8/2013  
 WO WO2013124415 A1 8/2013  
 WO WO2013127727 A1 9/2013  
 WO WO2013127728 A1 9/2013  
 WO WO2013144356 A1 10/2013

## US 8,987,237 B2

Page 10

(56)

## References Cited

## FOREIGN PATENT DOCUMENTS

WO	WO2013149258	A2	10/2013
WO	WO2013158454	A2	10/2013
WO	WO2013170052	A1	11/2013
WO	2013192248	A1	12/2013
WO	2013192249	A1	12/2013
WO	2013192250	A1	12/2013
WO	2013192251	A1	12/2013
WO	WO2013178587	A1	12/2013
WO	WO2013181449	A1	12/2013
WO	WO2014001904	A1	1/2014
WO	WO2014004424	A1	1/2014
WO	WO2014009434	A1	1/2014
WO	WO2014018569	A1	1/2014
WO	WO2014018570	A1	1/2014
WO	WO2014018571	A2	1/2014
WO	WO2014018856	A1	1/2014
WO	WO2014018932	A2	1/2014
WO	WO2014031958	A1	2/2014
WO	WO2014041120	A1	3/2014
WO	WO2014052792	A1	4/2014
WO	WO2014056897	A1	4/2014
WO	WO2014066442	A2	5/2014
WO	WO2014074846	A1	5/2014
WO	WO2014076231	A1	5/2014
WO	WO2014076569	A2	5/2014
WO	WO2014081598	A1	5/2014
WO	WO2014086739	A1	6/2014
WO	WO2014093114	A1	6/2014
WO	WO2014104784	A1	7/2014

## OTHER PUBLICATIONS

USPTO; Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002.

USPTO; Notice of Allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002.

Acarturk, "Mucoadhesive Vaginal Drug Delivery Systems," Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Exiler-Ankara, Recent Patents on Drug Delivery & Formulation 2009, 3, 193-205.

Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," Drug Development and Industrial Pharmacy, 35(5):525-547 (May 2009). Abstract Only.

Azure Pharma, Inc., "ELESTRIN™—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archived=11885>, 26 pages (Aug. 2009).

Bhavnani, et al., "Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ERA and ERβ", Endocrinology, 149(10): 4857-4870 (Oct. 2008).

Bhavnani, et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," J Clin Endocrinol Metab, Mar. 2012, 97(3).

Tahition Noni, "Body Balance Cream," [http://products.tni.com/dominican\\_republic/sa\\_spanish/nonistore/product/3438/3416/](http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/), (undated), 1 page.

Nugen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, (undated), 3 pages.

Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," J. Kor. Pharm. Sci., 35(3):173-177, (2005).

Committee of Obstetric Practice, Committee Opinion—No. 522, Obstetrics & Gynecology, 119(4):879-882 (Apr. 2012).

Diramio, "Polyethylene Glycol Methacrylate/Dimetacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia—Masters of Science Thesis, 131 pages (2004). [http://athenaum.libs.uga.edu/bitstream/handle/10724/7820/diramio\\_jackie\\_a\\_200412\\_ms.pdf?sequence=1](http://athenaum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1).

Du, et al., "Percutaneous Progesterone Delivery Via Cream or Gel Application in Postmenopausal Women: A Randomized Cross-Over Study of Progesterone Levels in Serum, Whole Blood, Saliva, and

Capillary Blood," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 11, (Feb. 2013).

Fotherby, K., "Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy," Contraception 1996;54:59-69.

Fuchs, et al., "The Effects of on Estrogen and Glycolic Acid Cream on the Fociol Skin of Postmenopausal Women: A Randomized Histologic Study," Pharmacology / Cosmetology, vol. 5, No. 1, 2006.

Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," International Journal of Pharmaceutics, 147(2):165-171 (Feb. 1997). Abstract Only.

Hargrove, et al., Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone, vol. 73, No. 4, pp. 606-612 Apr. 1989.

Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," Critical Reviews in Toxicology, 30(3):307-345 (2000).

Kincl, et al., "Increasing Oral Bioavailability of Progesterone by Formulation," Pergamon Press, Journal of Steroid Biochemistry, 1978, vol. 9, pp. 83-84.

Knuth et al., "Hydrogel Delivery Systems for Vaginal and Oral Applications: Formulation and Biological Considerations," Advanced Drug Delivery Reviews, 11(1-2):137-167 (Jul.-Aug. 1993). Abstract Only.

Lucy et al., "Gonadotropin-Releasing Hormone at Estrus: Luteinizing Hormone, Estradiol, and Progesterone During the Peri-estrus and Postinsemination Periods in Dairy Cattle," Biol. Reprod. 35(2):300-311 (1986). Abstract Only.

Position Statement, "Management of Symptomatic Vulvovaginal Atrophy: 2013 Position Statement of the North American Menopause Society," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 9, pp. 888-902, Jun. 2013.

NuGest 900™, <http://www.thehormoneshop.net/nugest900.htm>, (undated), 4 pages.

Panay, et al., "The 2013 British Menopause Society & Women's Health Concern Recommendations on Hormone Replacement Therapy," DOI: 0.1177/1754045313489645, [min.sagepub.com](http://min.sagepub.com). Menopause International: The Integrated Journal of Postreproductive Health 0(0):1-10, 2013.

Panchagnula et al., "Development and Evaluation of an Intracutaneous Depot Formulation of Corticosteroids Using Transcutol as a Cosolvent: In-Vitro, Ex-Vivo and In-Vivo Rat Studies," J Pharm Pharmacol. 43(9):609-614 (Sep. 1991). Abstract Only.

Patel, et al., "Transdermal Drug Delivery System: A Review," [www.thepharmajournal.com](http://www.thepharmajournal.com), vol. 1 No. 4 2012.

Saloe, "The physicochemical properties of oestradiol," Journal of Pharmaceutical & Biomedical Analysis, 5(7):635-648 (1987).

Sarrel, et al., "The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years," American Journal of Public Health, Published online ahead of print Jul. 18, 2013.

Shufelt, et al., "Hormone Therapy Dose, Formulation, Route of Delivery, and Risk of Cardiovascular Events in Women: Findings From the Women's Health Initiative Observational Study," Menopause: The Journal of the North American Menopause Society, vol. 21, No. 3, 2014.

Simon, et al., "Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet," The American College of Obstetricians and Gynecologists, vol. 112, No. 5, Nov. 2008.

Sitruk-Ware, et al., "Oral Micronized Progesterone," Department of Reproductive Endocrinology, vol. 36, No. 4, pp. 373-402, Oct. 1987.

Sitruk-Ware, et al., "Progestogens in Hormonal Replacement Therapy: New Molecules, Risks, and Benefits," Menopause: The Journal of the North American Menopause Society, vol. 9, No. 1, pp. 6-15, 2002.

Smith, et al., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens," JAMA Internal Medicine <http://archinte.jamanetwork.com>, Sep. 30, 2013.

Stanczyk, et al., "Ethinyl Estradiol and 17β-Estradiol in Combined Oral Contraceptives: Pharmacokinetics, Pharmacodynamics and Risk Assessment," Departments of Obstetrics and Gynecology and



## US 8,987,237 B2

Page 11

(56)

## References Cited

## OTHER PUBLICATIONS

- Preventive Medicine, University of Southern California Keck School of Medicine, Contraception 87 706-727, (2013).
- Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," Pharmaceutical Research, 21(2):201-230 (Feb. 2004).
- Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," Skin Pharmacol Physiol, 19:106-121 (2006). [http://www.nanobiotec.iqm.unicamp.br/download/Trommer\\_skin%20penetration-2006rev.pdf](http://www.nanobiotec.iqm.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf).
- Whitehead, et al., "Absorption and Metabolism of Oral Progesterone," The British Medical Journal, vol. 280, No. 6217, Mar. 22, 1980.
- Wood, et al., "Effects of Estradiol with Micronized Progesterone or Medroxyprogesterone Acetate on Risk Markers for Breast Cancer in Postmenopausal Monkeys," Springer Science+Business Media B.V., Breast Cancer Res Treat 101:125-134, (2007).
- USPTO; Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545.
- USPTO; Restriction/ Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562.
- USPTO; Restriction/ Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623.
- US 6,214,374, 04/2001, Schmirler et al. (withdrawn).
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Saffey Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of *Thevetia peruviana* and *Hura crepitans* Seed oils using GC-FID, Fountain Journal of Nat. and Appl. Sciences, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopocia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index>[Feb. 3, 2014 1:37:50 PM].
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.
- Corn Refiners Assoc, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Eqbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Ferrari, Roseli AP, et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, Sci. Agric., vol. 62(3), pp. 291-295, 2005, Piracicaba, Braz.
- Gunstone, Frank D, et al., Vegetable Oils in Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, Clean Techn Environ Policy, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, Obstetrics & Gynecology, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, Springerlink.com, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, Journal of Food Science, vol. 47, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Lauroyl Polyoxylglycerides, Saffey Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate—Corn Oil, Lot G0L404, Jul. 2013.
- Weber, E.J., Corn Lipids, Cereal Chem., vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, Drug Development and Industrial Pharmacy, Early Online, pp. 1-8, 2014, Informa Healthcare.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone, SciFinder Scholar Search, pp. 1-46, Feb 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Struhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M, et al., The light sensitivity of corticosteroids in crystalline form, Pharmaceutica acta Helvetiae, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S, et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , Intl. J. of Pharmaceut., vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, AAPS PharmSciTech, vol. 11, No. 3, Sep. 2010.
- USP Monographs: Progesterone, USP29, [www.pharmacopeia.cn/v29240/usp29nf24s0\\_m69870.html](http://www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html), search done: Feb. 25, 2014.
- Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . Fertility and Sterility, vol. 75(6) pp. 1065, Jun. 2001.
- Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, J. SteroidBiochem. Mol. Biol. (2013), Elsevier.
- Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, Thermochimica Acta 485, Elsevier, pp. 57, 2009.
- Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, J. of Pharmaceutical Sciences, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, Handbook of Aqueous Solubility Data, Solutions, pp. 1110-1111, CRC PRESS, Boca Raton, London, New York, Wash. D.C.
- Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, Journal of Steroid Biochem & Mol Biology, vol. 86 pp. 477-486, 2003.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, Jour. of Mol. Structure, Theochem, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, Jour. of Mol. Structure, Theochem vol. 425, pp. 171-179, 1998, Elsevier.

## US 8,987,237 B2

Page 12

(56)

## References Cited

## OTHER PUBLICATIONS

- Kuhnert-Brandstatter, M., Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , *Drug Development and Industrial Pharmacy*, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steroids, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G., et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , *Maturitas, The European Menopaus Journal*, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroidal conformation of 17 $\alpha$ - and 17 $\beta$ -estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17 $\beta$  and Progesterone Concentrations in Uterine Lymph and Systematic Blood . . . , *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, *Catalent Pharma Solutions*, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MONO1500003758.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between  $\alpha$ - and  $\beta$ - Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*, 35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://lxsr7.oru.edu/~alang/onsc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res.* vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17 $\beta$ -diol solvate: estradiol-methanol-water, *Crystal Structure Comm.*, *Intn'l Union of Crystallography*, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, *Schering Corporation*, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gisela L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012%20Patches\_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Salole, Eugene G., Estradiol, *Analytical Profiles of Drug Substances*, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Base . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, *SciFinder*, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- SciFinder Scholar Prednisone Chemical Properties, *SciFinder*, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, *SciFinder*, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, *SciFinder*, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), *Crystal Structure Comm.*, vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>.
- ACOG, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists, ACOG, No. 141, vol. 123, No. 1, Jan. 2014, Obstetrics & Gynecology.
- Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), *Scanning* vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, *SciFinder*, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.

## US 8,987,237 B2

Page 13

(56)

## References Cited

## OTHER PUBLICATIONS

- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, *Steroids*, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M., Pressure-tuning infrared and solution Raman spectroscopic studies of 17 $\beta$ -estradiol and several A-ring . . . , *Vibrational Spectroscopy* 8, Elsevier, pp. 263, 1995.
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, *Bollettino Chimico Farmaceutico*, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, *Acta Pharm. Jugosl.*, vol. 40 pp. 71-94, 1990.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Buray, Kenneth A., Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, *Am J Obstet Gynecol*, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Cendejas-Santana, G., et al., Growth and characterization of progesterone crystallites, *Revista Mexicana de Fisica*, 50, Suplemento 1 pp. 1-3, 2004.
- Cole, Wayne & Julian, Percy L., Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Commodari, Fernando, Comparison of 17 $\beta$ -estradiol structures from x-ray diffraction and solution NMR, *Magn. Reson. Chem.*, vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A., et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, *The Lancet*, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Dideberg, O., et al., Crystal data on progesterone (C<sub>21</sub>H<sub>30</sub>O<sub>2</sub>), desoxycorticosterone (C<sub>21</sub>H<sub>30</sub>O<sub>3</sub>), corticosterone (C<sub>21</sub>H<sub>30</sub>O<sub>4</sub>) and aldosterone . . . , *J. Appl. Cryst.* vol. 4 pp. 80, 1971.
- Drakulic, Branko J., Role of complexes formation between drugs and penetration enhancers in transdermal . . . , *Inter. Journal of Pharmaceutics*, Elsevier, vol. 363, pp. 40-49, 2009.
- Duax, William L., et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, *J. Am. Chem. Soc.*, vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R., et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , *J. Thermal Anal.*, vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, SciFinder, *Pharmaceutica Acta Helvetica*, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.
- Giron, D., Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, *Thermochimica Acta*, vol. 248 pp. 1-59, 1995, Elsevier.
- Giron-Forest, D., et al., Thermal analysis methods for pharmacopoeial materials, *J. Pharmaceutical & Biomedical Anal.*, vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, *Acta Cryst.*, vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Helbling, Ignacio M., et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, *Pharm Res.*, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, *Jour. of Mag. Resonance*, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, *Mol. Pharmacology*, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17 $\beta$ -Estradiol Solid Dispersions, *Pharmaceutical Development and Tech.*, vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Idder, Salima, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johnson, William S., et al., Racemic Progesterone, *Tetrahedron Letters* No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, *Drug Dev. & Indus. Pharm.*, vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Korkmaz, Filiz, Biophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyan, P.N., Stability indicating HPTLC method for the estimation of estradiol, *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminiewski, R., et al., EPR Study of the Stable Radical in a  $\gamma$ -Irradiated Single Crystal of Progesterone, *Jour. of Mag. Resonance*, vol. 46 pp. 300-305, 1982, Academic Press.
- PCCA, Apothogram, May 2014, pp. 1-14, Houston, TX.
- Abitec Corporation, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.
- Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," *Southern Medical Journal*, vol. 107, No. 7, Jul. 2014, pp. 433-436.
- Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," *Journal of Adolescent Health*, 2003; 32:183-186.
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," *Clinical Pharmacy*, 1990, vol. 9, No. 5, pp. 366-371.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," *Journal of Pharmaceutical Sciences*, vol. 86, No. 1, Jan. 1997, pp. 13-18.



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(56)

**References Cited**

**OTHER PUBLICATIONS**

Sasol Olefins & Surfactants GmbH, Excipients for Pharmaceuticals, 2010, 28 pages.

Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," Food and Chemical Toxicology, 72 (2014) pp. 40-50.

Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," Journal of Pharmaceutical Sciences, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.

ZRT Laboratory, Provider Data Sheet, About Dried Blood Spot Testing, 2014, 3 pages.

\* cited by examiner

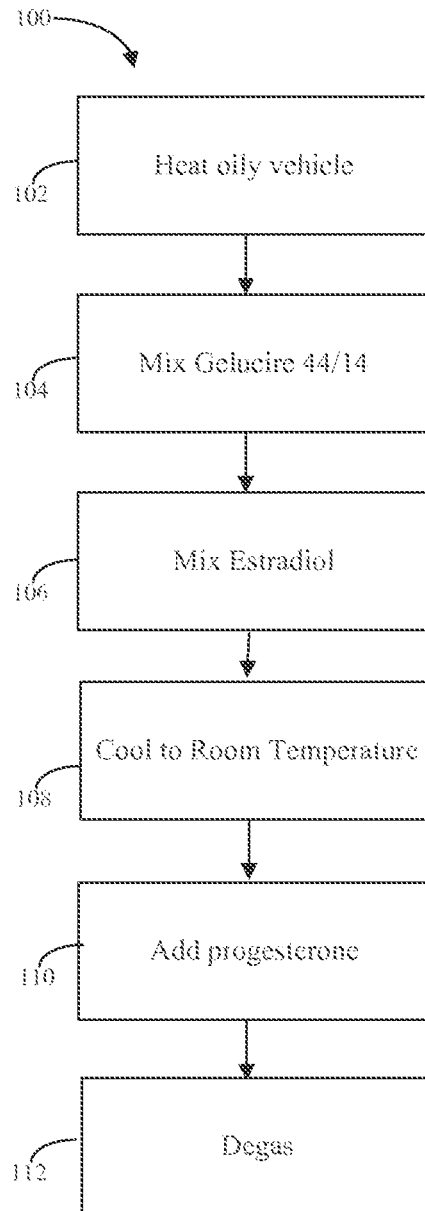
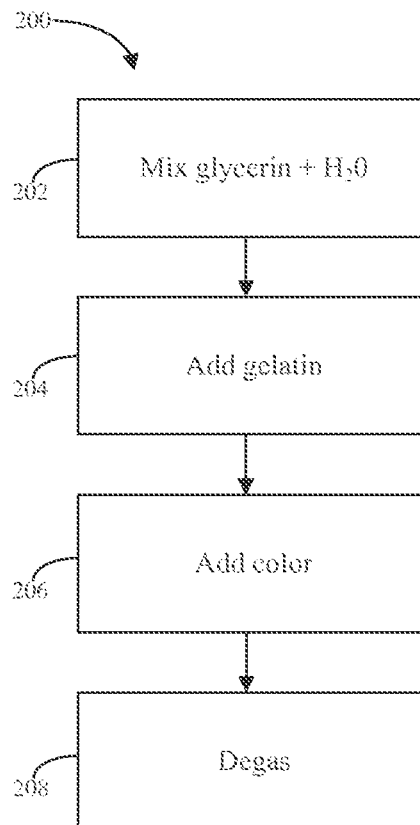
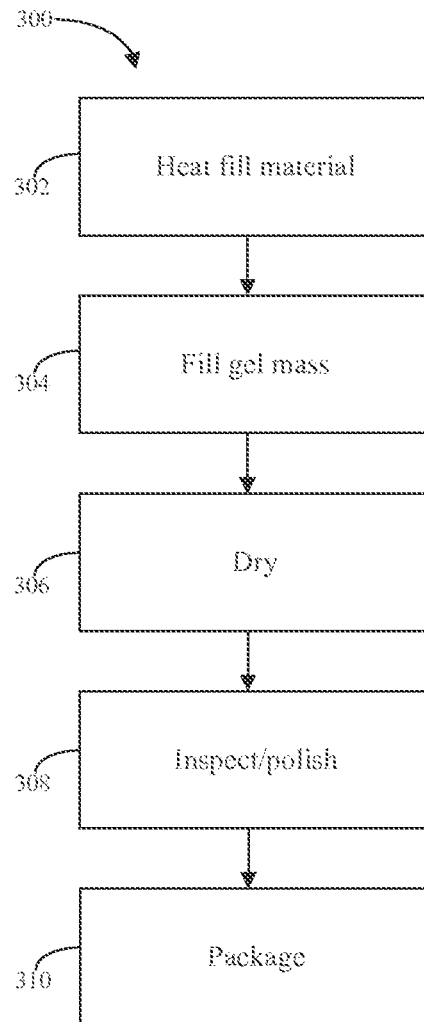


Fig. 1



**Fig. 2**



**Fig. 3**

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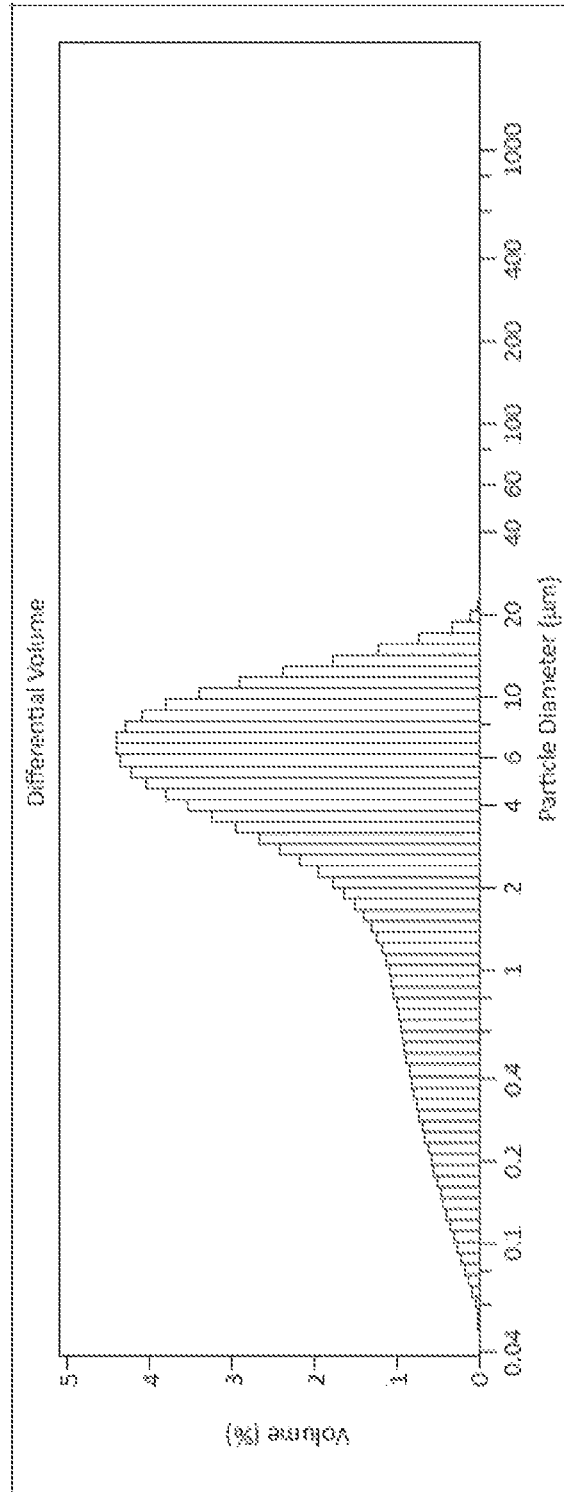


FIG. 4

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## NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

### CROSS REFERENCE TO RELATED APPLICATIONS

This application is a non-provisional application of and claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

### BACKGROUND

#### 1. Field

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

#### 2. Discussion of the Related Art

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

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"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as PREM-PRO (conjugated estrogens/medroxyprogesterone acetate tablets) and PREMPHASE (conjugated estrogens plus medroxyprogesterone acetate tablets) (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN (conjugated estrogens tablets) (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

### SUMMARY

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

### BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

### DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because



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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

#### DEFINITIONS

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to PROMETRIUM (progesterone, USP) at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC,  $C_{max}$ , and optionally,  $T_{max}$ .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ $C_{max}$ ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ $T_{max}$ ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC,  $C_{max}$  and, optionally,  $T_{max}$  are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to estab-

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lished governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

#### DESCRIPTION

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM (progesterone, USP) when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg:50 mg to about 2 mg:1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

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Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of PROMETRIUM (progesterone, USP). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM (progesterone, USP) at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM (progesterone, USP) can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 $\beta$ -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/

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sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017  $\mu$ m to 2000  $\mu$ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4  $\mu$ m to 2000  $\mu$ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These

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formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE (a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL (caprylic/capric triglyceride); SASOL Germany GMBH, Hamburg; MIGLYOL (caprylic/capric triglyceride) includes MIGLYOL 810 (Caprylic/Capric Triglyceride), MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 816 (Caprylic/Capric Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL PG-10 (Propylene Glycol Monocaprate); the CAPMUL brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM (Medium Chain Mono- and Diglycerides)); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL (diethylene glycol mono ester)); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL (caprylic/capric triglyceride); TRANSCUTOL (Diethylene glycol monoethyl ether), MIGLYOL (caprylic/capric triglyceride) and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant; and CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for full solubilization of progesterone. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. CAPMUL MCM (Medium Chain Mono- and Diglycerides) and GELUCIRE (a polyethylene glycol glyceride) can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

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Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxy-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may



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comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from errone-

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ous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

## EXAMPLES

### Example 1

#### Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL HP (Highly purified diethylene glycol monoethyl ether EP/NF)	141
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	31.2

\*Literature reference -Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

### Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL PG-8 (Propylene Glycol Monocaprylate) and CAPMUL MCM (Medium Chain Mono- and Diglycerides) by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) at 50%; and also CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL PG-8 (Propylene Glycol Monocaprylate) mixed with MIGLYOL (caprylic/capric triglyceride) at the 15 and 30% level did not provide sufficient solubility.

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TABLE 2

Ingredient	Solubility (mg/g)
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (85:15)	4.40
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	8.60
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	>12
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	>12
MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	14.0
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	19.8
Polysorbate 80:CAPMUL MCM (Medium Chain Mono- and Diglycerides) (20:80)	15.0

## Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. MIGLYOL 812 (Caprylic/Capric Triglyceride) with 4% TRANSCUTOL (Diethylene glycol monoethyl ether) precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL (a propylene glycol monocaprylate; propylene glycol monocaprylate) blends at 30 and 50% or in CAPMUL MCM (Medium Chain Mono- and Diglycerides) alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride) (4:96)	4	Crystallizes after 96 hours
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (70:30)	6	Clear, after 14 days
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	6	Clear, after 14 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:80:15)	6	Clear, after 14 days
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	6	Clear after 14 days

12 mg estradiol solubilized in MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) 50:50, CAPMUL MCM(Medium Chain Mono- and Diglycerides), and in mixtures of TRANSCUTOL (Diethylene glycol monoethyl ether): MIGLYOL (caprylic/capric triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) are stable and do not precipitate for at least 12 days.

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TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Clear, after 12 days
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Clear, after 12 days
CAPMUL MCM(Medium Chain Mono- and Diglycerides)	12	Clear after 12 days

## Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL MCM (Medium Chain Mono- and Diglycerides) are able to absorb a minimum of 7% water without recrystallization. All CAPMUL PG-8 (Propylene Glycol Monocaprylate) containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL PG-8 (Propylene Glycol Monocaprylate) alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (75:25)	6	Precipitated
MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (50:50)	12	Hazy
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:65:28)	12	Hazy
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	12	Clear

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TABLE 5-continued

Formulation	Estradiol mg/g	Results after addition of 7% water
TRANSCUTOL (Diethylene glycol monoethyl ether):MIGLYOL 812 (Caprylic/Capric Triglyceride):CAPMUL PG-8 (Propylene Glycol Monocaprylate) (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

## Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (TRANSCUTOL IHP (Highly purified diethylene glycol monoethyl ether EP/NF))	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

## Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved.

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## Example 7

## Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL (caprylic/capric triglyceride) was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL (caprylic/capric triglyceride) may be used in embodiments comprising a suspension of progesterone, though MIGLYOL (caprylic/capric triglyceride), standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM (Medium Chain Mono- and Diglycerides) is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL (caprylic/capric triglyceride) had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL MCM (Medium Chain Mono- and Diglycerides). It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL MCM (Medium Chain Mono- and Diglycerides).

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides)	73.4
CAPMUL PG-8 (Propylene Glycol Monocaprylate)	95
MIGLYOL 812 (Caprylic/ Capric Triglyceride)	27.8

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM (Medium Chain Mono- and Diglycerides) in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Gelucire 44/14 system, wherein the ratio of CAPMUL MCM (Medium Chain Mono- and Diglycerides) to GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is 9:1.



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TABLE 10

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (9:1)	86.4
CAPMUL MCM (Medium Chain Mono- and Diglycerides) GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (7:3)	70.5
CAPMUL MCM (Medium Chain Mono- and Diglycerides):GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) (6:4)	57.4

## Example 7

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97
GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL MCM (Medium Chain Mono- and Diglycerides) may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/- 2° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) may be added to the CAPMUL MCM (Medium Chain Mono- and Diglycerides) and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Heat may be removed from the GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) and CAPMUL MCM (Medium Chain Mono- and Diglycerides)

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mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, CAPMUL MCM (Medium Chain Mono- and Diglycerides) and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

## Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL (caprylic/capric triglyceride) is heated to about 45° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM (Medium Chain Mono- and Diglycerides))	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2%

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w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to about 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 (Caprylic/Capric Triglyceride) or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL (caprylic/capric triglyceride) may be present in a range from about 35-95% by weight; GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279  $\mu$ m, an X75 of 7.442  $\mu$ m, and an X25 of 1.590  $\mu$ m. The Beckman Device also yielded that the mean particle size is 4.975  $\mu$ m, the median particle size is 4.279  $\mu$ m, the mode particle size is 6.453  $\mu$ m, and the standard deviation is 3.956  $\mu$ m. A graph of the particle distribution obtained is shown in FIG. 4.

## Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0  $\mu$ m, an X75 of 17.3  $\mu$ m, and an X25 of 5.3  $\mu$ m. The Beckman Device also yielded that the mean particle size is 11.8  $\mu$ m, the median

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particle size is 11.04  $\mu$ m, the mode particle size is 13.6  $\mu$ m, and the standard deviation is 7.8  $\mu$ m.

## Example 12

In order to increase the solubility of progesterone in the final solution, GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules						
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)	
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50	
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02	
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		82.57	577.97	5.78	
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) Gelucire 44/14, NF		10.0	70.00	0.70	
Total:			100.00	700.00	7.00	

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 40° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

## Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		73.371	146.74	1467.42
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF		1.500	3.00	30.00

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TABLE 16-continued

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
	Lauroyl polyoxylglycerides (USA FDA IIG)), NF				
Total:		100.000	200.00 mg		2000.00

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)) is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	CAPMUL MCM (Medium Chain Mono- and Diglycerides), NF		65.32	391.93	3919.3
4.	GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), NF		1.00	6.0	60.0
Total:		100.00	600.0 mg		6000.0

The manufacturing process is as follows. CAPMUL MCM (Medium Chain Mono- and Diglycerides) is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 15

Progesterone and Estradiol Combination Study Under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM (progesterone, USP) (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

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The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM (progesterone, USP) soft gel Capsule 200 mg and ESTRACE (estradiol vaginal cream, USP, 0.01%) (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

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At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of  $-70^{\circ}\text{C} \pm 20^{\circ}\text{C}$  in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

#### Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to  $40^{\circ}\text{C} \pm 5^{\circ}\text{C}$ . Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL MCM (Medium Chain Mono- and Diglycerides).

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ .

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Heating may be performed until the temperature reaches  $80^{\circ}\text{C} \pm 5^{\circ}\text{C}$ .

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Step 208 comprises degassing. The

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resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to  $30^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes. Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of  $55^{\circ}\text{C} \pm 10^{\circ}\text{C}$ . The wedge temperature may be  $38^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . The drum cooling temperature may be  $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$ . The encapsulator may be lubricated using MIGLYOL 812 (Caprylic/Capric Triglyceride) or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness  $0.85\text{ mm} \pm 0.05\text{ mm}$  using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight  $\pm 5\%$  (i.e.,  $650 \pm 33\text{ mg}$  and  $325 \pm 16.3\text{ mg}$ ).

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of  $55^{\circ}\text{C} \pm 10^{\circ}\text{C}$ . The wedge temperature may be  $38^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . The drum cooling temperature may be  $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$ . The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness  $0.85\text{ mm} \pm 0.05\text{ mm}$  using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight  $\pm 5\%$  (i.e.,  $650 \pm 33\text{ mg}$  and  $325 \pm 16.3\text{ mg}$ ).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

We claim:

1. A pharmaceutical composition comprising:  
a solubilizing agent comprising:

mono- and diglycerides of capric and caprylic acid; and at least one of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, or lauroyl polyoxyglycerides;  
progesterone; and  
estradiol, the estradiol being at least about 90% solubilized in the solubilizing agent;  
wherein the estradiol and the progesterone are present in the solubilizing agent, and the estradiol and suspended progesterone are uniformly dispersed.

2. The pharmaceutical composition of claim 1, wherein the ratio of progesterone to estradiol is from about 24:1 to about 200:1.

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3. The pharmaceutical composition of claim 2, wherein the ratio of progesterone to estradiol comprises one of: about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, and about 200:1.

4. The pharmaceutical composition of claim 1, wherein the progesterone is between about 7.14% w/w and about 33.33% w/w of the pharmaceutical composition.

5. The pharmaceutical composition of claim 1, wherein the estradiol is between about 0.12% w/w and about 0.35% w/w of the pharmaceutical composition.

6. The pharmaceutical composition of claim 1, wherein the composition is encapsulated in a gelatin capsule; and wherein each gelatin capsule comprises from about 25 mg to about 200 mg of progesterone and from about 0.125 mg to about 2.00 mg of estradiol.

7. The pharmaceutical composition of claim 1, wherein the estradiol is at least 90% solubilized in the solubilizing agent.

8. A pharmaceutical composition comprising:  
a solubilizing agent comprising:  
monoglycerides and diglycerides of caprylic and capric acid; and

a polyethylene glycol glyceride;

progesterone; and

estradiol, the estradiol being at least about 90% solubilized in the solubilizing agent;

wherein the estradiol and the progesterone are present in the solubilizing agent, and the estradiol and progesterone are uniformly dispersed.

9. The pharmaceutical composition of claim 8, wherein the ratio of progesterone to estradiol is from about 24:1 to about 200:1.

10. The pharmaceutical composition of claim 9, wherein the ratio of progesterone to estradiol comprises one of: about 24:1, about 25:1, about 96:1, about 100:1, about 192:1 and about 200:1.

11. The pharmaceutical composition of claim 8, wherein the progesterone is between about 7.14% w/w and about 33.33% w/w of the pharmaceutical composition.

12. The pharmaceutical composition of claim 8, wherein the estradiol is between about 0.12% w/w and about 0.35% w/w of the pharmaceutical composition.

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13. The pharmaceutical composition of claim 8, wherein the composition is encapsulated in a gelatin capsule; and wherein each gelatin capsule comprises from about 25 mg to about 200 mg of progesterone and from about 0.125 mg to about 2.00 mg of estradiol.

14. The pharmaceutical composition of claim 8, wherein the estradiol is at least 90% solubilized in the solubilizing agent.

15. A pharmaceutical composition comprising:

a solubilizing agent comprising:

mono- and diglycerides of capric and caprylic acid; and at least one of lauroyl macrogol-32 glycerides, lauroyl polyoxyl-32 glycerides, and lauroyl polyoxylglycerides;

progesterone; and

estradiol, the estradiol being at least about 90% solubilized in the solubilizing agent;

wherein the estradiol and the suspended progesterone are present in the solubilizing agent, and the estradiol and suspended progesterone are uniformly.

16. The pharmaceutical composition of claim 15, wherein the ratio of progesterone to estradiol is from about 24:1 to about 200:1.

17. The pharmaceutical composition of claim 15, wherein the ratio of progesterone to estradiol comprises one of: about 24:1, about 25:1, about 96:1, about 100:1, about 192:1 and about 200:1.

18. The pharmaceutical composition of claim 15, wherein the progesterone is between about 7.14% w/w and about 33.33% w/w of the pharmaceutical composition.

19. The pharmaceutical composition of claim 15, wherein the estradiol is between about 0.12% w/w and about 0.35% w/w of the pharmaceutical composition.

20. The pharmaceutical composition of claim 15, wherein the composition is encapsulated in a gelatin capsule; and wherein each gelatin capsule comprises from about 25 mg to about 200 mg of progesterone and from about 0.125 mg to about 2.00 mg of estradiol.

\* \* \* \* \*



UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,987,237 B2  
APPLICATION NO. : 14/099562  
DATED : March 24, 2015  
INVENTOR(S) : Brian A. Bernick et al.

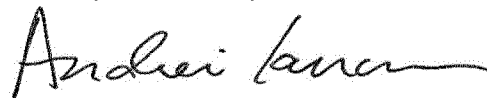
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this  
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu  
*Director of the United States Patent and Trademark Office*



UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,987,237 B2  
APPLICATION NO. : 14/099562  
DATED : March 24, 2015  
INVENTOR(S) : Brian A. Bernick et al.

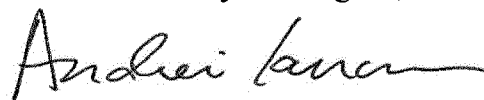
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 24, Claim 15, Line 21: Insert --dispersed-- after “uniformly”.

Signed and Sealed this  
Twentieth Day of August, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu", written in a cursive style.

Andrei Iancu  
*Director of the United States Patent and Trademark Office*

# EXHIBIT E



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(12) **United States Patent**  
**Bernick et al.**

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(54) **NATURAL COMBINATION HORMONE  
REPLACEMENT FORMULATIONS AND  
THERAPIES**

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

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2,232,438	A	2/1941	Butenandt	
4,900,734	A *	2/1990	Maxson et al.	514/171
5,538,736	A	7/1996	Hoffmann et al.	
5,556,635	A	9/1996	Istin et al.	
5,580,572	A	12/1996	Mikler et al.	
5,605,702	A	2/1997	Teillaud et al.	
5,607,691	A	3/1997	Hale et al.	
5,607,693	A	3/1997	Bonte et al.	
5,609,617	A	3/1997	Shealy et al.	
5,626,866	A	5/1997	Ebert et al.	
5,653,983	A	8/1997	Meybeck et al.	
5,660,839	A	8/1997	Allec et al.	
5,662,927	A	9/1997	Ehrlich et al.	
5,663,160	A	9/1997	Meybeck et al.	
5,686,097	A	11/1997	Taskovich et al.	
5,693,335	A	12/1997	Xia et al.	
5,700,480	A	12/1997	Hille et al.	
5,719,197	A	2/1998	Kanios et al.	
5,770,220	A	6/1998	Meconi et al.	
5,770,227	A	6/1998	Dong et al.	
5,780,044	A	7/1998	Yewey et al.	
5,780,050	A	7/1998	Jain et al.	
5,788,984	A	8/1998	Guenther et al.	
5,820,878	A	10/1998	Hirano et al.	
5,840,327	A	11/1998	Gale et al.	
5,843,468	A	12/1998	Burkoth et al.	
5,843,979	A	12/1998	Wille et al.	
5,858,394	A	1/1999	Lipp et al.	
5,863,552	A	1/1999	Yue	

(Continued)

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**FOREIGN PATENT DOCUMENTS**

WO	WO9619975	7/1996
WO	WO0241878	5/2002

(Continued)

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**OTHER PUBLICATIONS**

Abitec Corporation, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.  
Corbett et al., “Trends in Pharmacy Compounding for Women’s Health in North Carolina: Focus on Vulvodynia,” Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.  
Shrier et al., “Mucosal Immunity of the Adolescent Female Genital Tract,” Journal of Adolescent Health, 2003; 32:183-186.  
Gattefossé Sas, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.  
Gattefossé Sas, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.  
Gattefossé Sas, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.

(Continued)

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(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

**6 Claims, 4 Drawing Sheets**

## US 8,993,548 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

5,882,676	A	3/1999	Lee et al.	7,094,228	B2	8/2006	Zhang et al.
5,885,612	A	3/1999	Meconi et al.	7,097,853	B1	8/2006	Garbe et al.
5,888,533	A	3/1999	Dunn	7,105,573	B2	9/2006	Krajcik et al.
5,891,462	A	4/1999	Carrara	7,153,522	B1	12/2006	Ikeura et al.
5,902,603	A	5/1999	Chen et al.	7,175,850	B2	2/2007	Cevc
5,904,931	A	5/1999	Lipp et al.	7,198,800	B1	4/2007	Ko
5,906,830	A	5/1999	Farinas et al.	7,381,427	B2	6/2008	Ancira et al.
5,912,010	A	6/1999	Wille et al.	7,456,159	B2	11/2008	Houze et al.
5,919,477	A	7/1999	Bevan et al.	7,498,303	B2	3/2009	Arnold et al.
5,942,243	A	8/1999	Shah	7,534,780	B2	5/2009	Wyrwa et al.
5,952,000	A	9/1999	Venkateshwaran et al.	7,569,274	B2	8/2009	Besse et al.
5,968,919	A	10/1999	Samour et al.	7,799,769	B2	9/2010	White et al.
5,985,311	A	11/1999	Cordes et al.	7,815,936	B2	10/2010	Hasenzahl et al.
5,985,850	A	11/1999	Falk et al.	7,829,116	B2	11/2010	Griswold et al.
5,989,568	A	11/1999	Breton et al.	7,850,992	B2	12/2010	Kim et al.
6,007,835	A	12/1999	Bon Lapillonne et al.	7,854,753	B2	12/2010	Kraft et al.
6,010,715	A	1/2000	Wick et al.	7,871,643	B2	1/2011	Lizio et al.
6,013,276	A	1/2000	Math et al.	7,960,368	B2	6/2011	Nickisch et al.
6,024,974	A	2/2000	Li	8,048,017	B2	11/2011	Xu
6,030,948	A	2/2000	Mann	8,063,030	B2	11/2011	Ellman
6,040,340	A	3/2000	Chwalisz et al.	8,071,576	B2	12/2011	Coelingh Bennink et al.
6,068,853	A	5/2000	Giannos et al.	8,075,916	B2	12/2011	Song et al.
6,087,352	A	7/2000	Trout	8,075,917	B2	12/2011	Chung et al.
6,090,404	A	7/2000	Meconi et al.	8,076,317	B2	12/2011	Kulmann
6,106,848	A	8/2000	Preuilh et al.	8,080,553	B2	12/2011	Keith et al.
6,124,362	A	9/2000	Bradbury et al.	8,096,940	B2	1/2012	Josephson et al.
6,139,868	A	10/2000	Hoffmann	8,114,152	B2	2/2012	Furst
6,149,935	A	11/2000	Chiang et al.	8,114,442	B2	2/2012	Tucker et al.
6,187,323	B1	2/2001	Aiache et al.	8,119,741	B2	2/2012	Pavlin
6,217,886	B1	4/2001	Onyuksel et al.	8,124,118	B2	2/2012	Lennernas et al.
6,225,297	B1	5/2001	Stockemann et al.	8,124,595	B2	2/2012	Boissonneault
6,228,383	B1	5/2001	Hansen et al.	8,147,561	B2	4/2012	Binmoeller
6,228,852	B1	5/2001	Shaak	8,148,546	B2	4/2012	Schuster et al.
6,242,509	B1	6/2001	Berger et al.	8,158,613	B2	4/2012	Staniforth et al.
6,245,811	B1	6/2001	Horrobin et al.	8,163,722	B2	4/2012	Savoir et al.
6,267,984	B1	7/2001	Beste et al.	8,177,449	B2	5/2012	Bayly et al.
6,274,165	B1	8/2001	Meconi et al.	8,187,615	B2	5/2012	Friedman
6,303,132	B1	10/2001	Nelson	8,195,403	B2	6/2012	Ishikawa et al.
6,303,588	B1	10/2001	Danielov	8,221,785	B2	7/2012	Chien
6,312,703	B1	11/2001	Orthoefer	8,222,237	B2	7/2012	Nickisch et al.
6,328,987	B1	12/2001	Marini	8,257,724	B2	9/2012	Cromack et al.
6,344,211	B1	2/2002	Hille	8,257,725	B2	9/2012	Cromack et al.
6,372,245	B1	4/2002	Bowman et al.	8,268,352	B2	9/2012	Vaya et al.
6,420,352	B1	7/2002	Knowles	8,268,806	B2	9/2012	Labrie
6,432,438	B1	8/2002	Shukla	8,268,878	B2	9/2012	Armer et al.
6,451,300	B1	9/2002	Dunlop et al.	8,288,366	B2	10/2012	Chochinov et al.
6,465,004	B1	10/2002	Rossi Montero et al.	8,318,898	B2	11/2012	Fasel et al.
6,465,005	B1	10/2002	Biali et al.	8,324,193	B2	12/2012	Lee-Sepsick et al.
6,465,006	B1	10/2002	Zhang et al.	8,337,814	B2	12/2012	Osbakken et al.
6,495,160	B2	12/2002	Esposito et al.	8,344,007	B2	1/2013	Tang et al.
6,521,250	B2	2/2003	Meconi et al.	8,353,863	B2	1/2013	Imran
6,531,149	B1	3/2003	Kirstgen et al.	8,357,723	B2	1/2013	Satyam
6,538,039	B2	3/2003	Laurent	8,361,995	B2	1/2013	Schramm
6,548,053	B1	4/2003	Stewart et al.	8,362,091	B2	1/2013	Tamarkin et al.
6,555,131	B1	4/2003	Wolff et al.	8,372,424	B2	2/2013	Berry et al.
6,562,367	B1	5/2003	Wolff et al.	8,372,806	B2	2/2013	Boehler et al.
6,562,370	B2	5/2003	Luo et al.	8,377,482	B2	2/2013	Laurie et al.
6,562,790	B2	5/2003	Chein	8,377,994	B2	2/2013	Gray et al.
6,599,519	B1	7/2003	Seo et al.	8,394,759	B2	3/2013	Barathur et al.
6,610,674	B1	8/2003	Schreiber	8,415,332	B2	4/2013	Diliberti et al.
6,635,274	B1	10/2003	Masiz et al.	8,435,972	B2	5/2013	Stein et al.
6,638,528	B1	10/2003	Kanios	8,449,879	B2	5/2013	Laurent Applegate et al.
6,649,155	B1	11/2003	Dunlop et al.	8,450,108	B2	5/2013	Boyce
6,682,757	B1	1/2004	Wright	8,454,945	B2	6/2013	McCook et al.
6,708,822	B1	3/2004	Muni	8,455,468	B2	6/2013	Hoffman et al.
6,720,001	B2	4/2004	Chen et al.	8,461,138	B2	6/2013	Boissonneault
6,743,448	B2	6/2004	Kryger	8,476,252	B2	7/2013	Achleitner et al.
6,750,291	B2	6/2004	Kim et al.	8,481,488	B2	7/2013	Carter
6,821,524	B2	11/2004	Marini	8,486,374	B2	7/2013	Tamarkin et al.
6,911,211	B2	6/2005	Eini et al.	8,486,442	B2	7/2013	Matsushita et al.
6,960,337	B2	11/2005	Daniels et al.	8,492,368	B2	7/2013	Vanlandingham et al.
6,974,569	B2	12/2005	Dunlop et al.	8,507,467	B2	8/2013	Matsui et al.
6,995,149	B1	2/2006	Endrikat et al.	8,512,693	B2	8/2013	Capito et al.
7,004,321	B1	2/2006	Palm et al.	8,512,754	B2	8/2013	Needham
7,030,104	B2	4/2006	Gray et al.	8,518,376	B2	8/2013	Tamarkin et al.
				8,536,159	B2	9/2013	Li et al.
				8,540,967	B2	9/2013	Barrett et al.
				8,541,400	B2	9/2013	Johnsson et al.
				8,551,462	B2	10/2013	Goldstein et al.

## US 8,993,548 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

8,557,281	B2	10/2013	Halliday et al.	2005/0186141	A1	8/2005	Gonda et al.
8,568,374	B2	10/2013	De Graaff et al.	2005/0196434	A1	9/2005	Brierre
8,591,951	B2	11/2013	Kohn et al.	2005/0220900	A1	10/2005	Popp et al.
8,613,951	B2	12/2013	Zale et al.	2005/0239747	A1	10/2005	Yang et al.
8,633,178	B2	1/2014	Bernick et al.	2005/0239758	A1	10/2005	Roby
8,633,180	B2	1/2014	Li et al.	2005/0244360	A1	11/2005	Billoni
8,636,787	B2	1/2014	Sabaria	2005/0266088	A1	12/2005	Hinrichs et al.
8,636,982	B2	1/2014	Tamarkin et al.	2005/0271597	A1	12/2005	Keith
8,653,129	B2	2/2014	Fein et al.	2005/0272685	A1	12/2005	Hung
8,658,627	B2	2/2014	Voskuhl	2006/0009428	A1	1/2006	Grubb et al.
8,663,692	B1	3/2014	Mueller et al.	2006/0034904	A1	2/2006	Weimann
8,663,703	B2	3/2014	Lerner et al.	2006/0078618	A1	4/2006	Constantinides et al.
8,664,207	B2	3/2014	Li et al.	2006/0084704	A1	4/2006	Shih et al.
8,669,293	B2	3/2014	Levy et al.	2006/0088580	A1	4/2006	Meconi et al.
8,679,552	B2	3/2014	Guthery	2006/0100180	A1	5/2006	Nubbemeyer et al.
8,697,127	B2	4/2014	Sah	2006/0121102	A1	6/2006	Chiang
8,697,710	B2	4/2014	Li et al.	2006/0165744	A1	7/2006	Jamil et al.
8,703,105	B2	4/2014	Tamarkin et al.	2006/0193789	A1	8/2006	Tamarkin et al.
8,709,385	B2	4/2014	Tamarkin et al.	2006/0233743	A1	10/2006	Kelly
8,709,451	B2	4/2014	Nam et al.	2006/0233841	A1	10/2006	Brodbeck et al.
8,715,735	B2	5/2014	Funke et al.	2006/0246122	A1	11/2006	Langguth et al.
8,721,331	B2	5/2014	Raghuprasad	2006/0247221	A1	11/2006	Coelingh Bennink et al.
8,722,021	B2	5/2014	Friedman et al.	2006/0251581	A1	11/2006	McIntyre et al.
8,734,846	B2	5/2014	Ali et al.	2006/0275218	A1	12/2006	Tamarkin et al.
8,735,381	B2	5/2014	Podolski	2006/0276414	A1	12/2006	Coelingh Bennink et al.
8,741,336	B2	6/2014	Dipierro et al.	2006/0292223	A1	12/2006	Woolfson et al.
8,741,373	B2	6/2014	Bromley et al.	2007/0009559	A1	1/2007	Li et al.
8,753,661	B2	6/2014	Steinmueller Nethl et al.	2007/0009594	A1	1/2007	Grubb et al.
8,784,882	B2	7/2014	Mattern	2007/0010550	A1	1/2007	McKenzie
2001/0009673	A1	7/2001	Lipp et al.	2007/0014839	A1	1/2007	Bracht
2001/0023261	A1	9/2001	Ryoo et al.	2007/0015698	A1	1/2007	Kleinman et al.
2001/0053383	A1	12/2001	Miranda et al.	2007/0037780	A1	2/2007	Ebert et al.
2002/0035070	A1	3/2002	Gardlik et al.	2007/0037782	A1	2/2007	Hibino et al.
2002/0119174	A1	8/2002	Gardlik et al.	2007/0078091	A1	4/2007	Hubler et al.
2002/0119198	A1	8/2002	Gao et al.	2007/0128263	A1	6/2007	Gargiulo et al.
2002/0142017	A1	10/2002	Simonnet	2007/0154533	A1	7/2007	Dudley
2002/0169205	A1	11/2002	Chwalisz et al.	2007/0167418	A1	7/2007	Ferguson
2002/0193758	A1	12/2002	Sandberg	2007/0185068	A1	8/2007	Ferguson et al.
2002/0197286	A1	12/2002	Brandman et al.	2007/0190022	A1	8/2007	Bacopoulos et al.
2003/0003139	A1	1/2003	Lipp et al.	2007/0196415	A1	8/2007	Chen et al.
2003/0027772	A1	2/2003	Breton	2007/0232574	A1	10/2007	Galey et al.
2003/0044453	A1	3/2003	Dittgen et al.	2007/0248658	A1	10/2007	Zurdo Schroeder et al.
2003/0091620	A1	5/2003	Fikstad et al.	2007/0254858	A1	11/2007	Cronk
2003/0109507	A1	6/2003	Franke et al.	2007/0255197	A1	11/2007	Humberstone et al.
2003/0113268	A1	6/2003	Buenafoe et al.	2007/0287688	A1	12/2007	Chan et al.
2003/0170295	A1	9/2003	Kim et al.	2007/0292359	A1	12/2007	Friedman et al.
2003/0175329	A1	9/2003	Azarnoff et al.	2007/0292461	A1	12/2007	Tamarkin et al.
2003/0175333	A1	9/2003	Shefer et al.	2007/0292493	A1	12/2007	Brierre
2003/0219402	A1	11/2003	Rutter	2007/0298089	A1	12/2007	Saeki et al.
2003/0225047	A1	12/2003	Caubel et al.	2008/0026040	A1	1/2008	Farr et al.
2003/0225048	A1	12/2003	Caubel et al.	2008/0038219	A1	2/2008	Mosbaugh et al.
2003/0235596	A1	12/2003	Gao et al.	2008/0039405	A1	2/2008	Langley et al.
2003/0236236	A1	12/2003	Chen et al.	2008/0050317	A1	2/2008	Tamarkin et al.
2004/0022820	A1	2/2004	Anderson	2008/0051351	A1	2/2008	Ghisalberti
2004/0039356	A1	2/2004	Maki et al.	2008/0063607	A1	3/2008	Tamarkin et al.
2004/0043043	A1	3/2004	Schlyter et al.	2008/0069779	A1	3/2008	Tamarkin et al.
2004/0048900	A1	3/2004	Flood	2008/0069791	A1	3/2008	Beissert
2004/0087564	A1	5/2004	Wright et al.	2008/0095831	A1	4/2008	Mc Graw
2004/0092494	A9	5/2004	Dudley	2008/0138390	A1	6/2008	Hsu et al.
2004/0110732	A1	6/2004	Masini Eteve et al.	2008/0139392	A1	6/2008	Acosta Zara et al.
2004/0138103	A1	7/2004	Patt	2008/0153789	A1	6/2008	Dmowski et al.
2004/0146539	A1	7/2004	Gupta	2008/0175905	A1	7/2008	Liu et al.
2004/0161435	A1	8/2004	Gupta	2008/0175908	A1	7/2008	Liu et al.
2004/0191207	A1	9/2004	Lipari et al.	2008/0206156	A1	8/2008	Cronk
2004/0210280	A1	10/2004	Liedtke	2008/0206159	A1	8/2008	Tamarkin et al.
2004/0219124	A1	11/2004	Gupta	2008/0214512	A1	9/2008	Seitz et al.
2004/0225140	A1	11/2004	Fernandez et al.	2008/0226698	A1	9/2008	Tang et al.
2004/0241219	A1	12/2004	Hille et al.	2008/0227763	A1	9/2008	Lanquetin et al.
2005/0003003	A1	1/2005	Basu et al.	2008/0234240	A1	9/2008	Duesterberg et al.
2005/0014729	A1	1/2005	Pulaski	2008/0261931	A1	10/2008	Hedner et al.
2005/0020550	A1	1/2005	Morris et al.	2009/0004246	A1	1/2009	Woolfson et al.
2005/0054991	A1	3/2005	Tobyn et al.	2009/0010968	A1	1/2009	Allart et al.
2005/0118244	A1	6/2005	Theobald et al.	2009/0011041	A1	1/2009	Musaeva et al.
2005/0129756	A1	6/2005	Podhaisky et al.	2009/0017120	A1	1/2009	Trimble et al.
2005/0152956	A1	7/2005	Dudley	2009/0022683	A1	1/2009	Song et al.
				2009/0047357	A1	2/2009	Tomohira et al.
				2009/0060997	A1	3/2009	Seitz et al.
				2009/0081206	A1	3/2009	Leibovitz
				2009/0093440	A1	4/2009	Murad

## US 8,993,548 B2

Page 4

(56)	<b>References Cited</b>		2012/0129773	A1	5/2012	Geier et al.
	U.S. PATENT DOCUMENTS		2012/0129819	A1	5/2012	Vancaillie et al.
			2012/0136013	A1	5/2012	Li et al.
			2012/0142645	A1	6/2012	Marx
2009/0098069	A1	4/2009	2012/0148670	A1	6/2012	Kim et al.
2009/0099149	A1	4/2009	2012/0172343	A1	7/2012	Lindenthal et al.
2009/0130029	A1	5/2009	2012/0184515	A1	7/2012	Klar et al.
2009/0175799	A1	7/2009	2012/0231052	A1	9/2012	Sitruk Ware et al.
2009/0186081	A1	7/2009	2012/0232011	A1	9/2012	Kneissel et al.
2009/0197843	A1	8/2009	2012/0232042	A1	9/2012	Klar et al.
2009/0203658	A1	8/2009	2012/0263679	A1	10/2012	Marlow et al.
2009/0227550	A1	9/2009	2012/0277249	A1	11/2012	Andersson et al.
2009/0285869	A1	11/2009	2012/0277727	A1	11/2012	Doshi et al.
2009/0324714	A1	12/2009	2012/0295911	A1	11/2012	Mannion et al.
2010/0008985	A1	1/2010	2012/0301517	A1	11/2012	Zhang et al.
2010/0034838	A1	2/2010	2012/0301538	A1	11/2012	Gordon Beresford et al.
2010/0034880	A1	2/2010	2012/0302535	A1	11/2012	Caufriez et al.
2010/0055138	A1	3/2010	2012/0316130	A1	12/2012	Hendrix
2010/0086501	A1	4/2010	2012/0316496	A1	12/2012	Hoffmann et al.
2010/0119585	A1	5/2010	2012/0321579	A1	12/2012	Edelson et al.
2010/0143420	A1	6/2010	2012/0322779	A9	12/2012	Voskuhl
2010/0143481	A1	6/2010	2012/0328549	A1	12/2012	Edelson et al.
2010/0150993	A1	6/2010	2012/0329738	A1	12/2012	Liu
2010/0204326	A1	8/2010	2013/0004619	A1	1/2013	Chow et al.
2010/0210994	A1	8/2010	2013/0011342	A1	1/2013	Tamarkin et al.
2010/0221195	A1	9/2010	2013/0017239	A1	1/2013	Viladot Petit et al.
2010/0227797	A1	9/2010	2013/0023505	A1	1/2013	Garfield et al.
2010/0247482	A1	9/2010	2013/0023823	A1	1/2013	Simpson et al.
2010/0247635	A1	9/2010	2013/0028850	A1	1/2013	Tamarkin et al.
2010/0273730	A1	10/2010	2013/0029957	A1	1/2013	Giliyar et al.
2010/0278759	A1	11/2010	2013/0045266	A1	2/2013	Choi et al.
2010/0279988	A1	11/2010	2013/0045953	A1	2/2013	Sitruk Ware et al.
2010/0291191	A1	11/2010	2013/0059795	A1	3/2013	Lo et al.
2010/0292199	A1	11/2010	2013/0064897	A1	3/2013	Binay
2010/0322884	A1	12/2010	2013/0072466	A1	3/2013	Choi et al.
2011/0039814	A1	2/2011	2013/0084257	A1	4/2013	Ishida et al.
2011/0087192	A1	4/2011	2013/0085123	A1	4/2013	Li et al.
2011/0098258	A1	4/2011	2013/0089574	A1	4/2013	Schmidt Gollwitzer et al.
2011/0104268	A1	5/2011	2013/0090318	A1	4/2013	Ulmann et al.
2011/0130372	A1	6/2011	2013/0102781	A1	4/2013	Bevill et al.
2011/0142945	A1	6/2011	2013/0108551	A1	5/2013	Langereis et al.
2011/0152840	A1	6/2011	2013/0116215	A1	5/2013	Coma et al.
2011/0158920	A1	6/2011	2013/0116222	A1	5/2013	Arnold et al.
2011/0171140	A1	7/2011	2013/0122051	A1	5/2013	Abidi et al.
2011/0190201	A1	8/2011	2013/0123175	A1	5/2013	Hill et al.
2011/0195031	A1	8/2011	2013/0123220	A1	5/2013	Queiroz
2011/0238003	A1	9/2011	2013/0123351	A1	5/2013	Dewitt
2011/0244043	A1	10/2011	2013/0131027	A1	5/2013	Pakkalin et al.
2011/0250256	A1	10/2011	2013/0131028	A1	5/2013	Snyder et al.
2011/0250259	A1	10/2011	2013/0131029	A1	5/2013	Bakker et al.
2011/0262373	A1	10/2011	2013/0149314	A1	6/2013	Bullerdiek et al.
2011/0275584	A1	11/2011	2013/0164225	A1	6/2013	Tamarkin et al.
2011/0281832	A1	11/2011	2013/0164346	A1	6/2013	Lee et al.
2011/0287094	A1	11/2011	2013/0165744	A1	6/2013	Carson et al.
2011/0294738	A1	12/2011	2013/0178452	A1	7/2013	King
2011/0300167	A1	12/2011	2013/0183254	A1	7/2013	Zhou et al.
2011/0301087	A1	12/2011	2013/0183325	A1	7/2013	Bottoni et al.
2011/0306579	A1	12/2011	2013/0189193	A1	7/2013	Tamarkin et al.
2011/0318405	A1	12/2011	2013/0189196	A1	7/2013	Tamarkin et al.
2011/0318431	A1	12/2011	2013/0189230	A1	7/2013	Shoichet et al.
2012/0021041	A1	1/2012	2013/0189368	A1	7/2013	Mosqueira et al.
2012/0028888	A1	2/2012	2013/0210709	A1	8/2013	McMurry et al.
2012/0028910	A1	2/2012	2013/0216550	A1	8/2013	Penninger et al.
2012/0028936	A1	2/2012	2013/0216596	A1	8/2013	Viladot Petit et al.
2012/0046264	A1	2/2012	2013/0224177	A1	8/2013	Kim et al.
2012/0046518	A1	2/2012	2013/0224257	A1	8/2013	Sah et al.
2012/0058171	A1	3/2012	2013/0224268	A1	8/2013	Alam et al.
2012/0058962	A1	3/2012	2013/0224300	A1	8/2013	Maggio
2012/0058979	A1	3/2012	2013/0225412	A1	8/2013	Sardari Lodriche et al.
2012/0064135	A1	3/2012	2013/0225542	A1	8/2013	Poegh et al.
2012/0065179	A1	3/2012	2013/0226113	A1	8/2013	Schumacher et al.
2012/0087872	A1	4/2012	2013/0243696	A1	9/2013	Wang et al.
2012/0101073	A1	4/2012	2013/0245253	A1	9/2013	Marx et al.
2012/0121517	A1	5/2012	2013/0245570	A1	9/2013	Jackson
2012/0121692	A1	5/2012	2013/0261096	A1	10/2013	Merian et al.
2012/0122829	A1	5/2012	2013/0266645	A1	10/2013	Becker et al.
2012/0128654	A1	5/2012	2013/0267485	A1	10/2013	Da Silva Maia Filho
2012/0128683	A1	5/2012	2013/0273167	A1	10/2013	Lee et al.
2012/0128733	A1	5/2012	2013/0274211	A1	10/2013	Burman et al.



## US 8,993,548 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

2013/0280213	A1	10/2013	Voskuhl
2013/0316374	A1	11/2013	Penninger et al.
2013/0317065	A1	11/2013	Tatani et al.
2013/0317315	A1	11/2013	Lu et al.
2013/0324565	A1	12/2013	Li et al.
2013/0331363	A1	12/2013	Li et al.
2013/0338124	A1	12/2013	Li et al.
2013/0345187	A1	12/2013	Rodriguez Oquendo
2014/0018335	A1	1/2014	Tatani et al.
2014/0024590	A1	1/2014	Weidhaas et al.
2014/0031289	A1	1/2014	Song et al.
2014/0031323	A1	1/2014	Perez
2014/0066416	A1	3/2014	Leunis et al.
2014/0072531	A1	3/2014	Kim et al.
2014/0079686	A1	3/2014	Barman et al.
2014/0088058	A1	3/2014	Maurizio
2014/0088059	A1	3/2014	Perumal et al.
2014/0094426	A1	4/2014	Drummond et al.
2014/0100159	A1	4/2014	Conrad
2014/0100206	A1	4/2014	Bernick et al.
2014/0113889	A1	4/2014	Connor et al.
2014/0127185	A1	5/2014	Stein et al.
2014/0127280	A1	5/2014	Duesterberg et al.
2014/0127308	A1	5/2014	Opara et al.
2014/0128798	A1	5/2014	Janson et al.
2014/0148491	A1	5/2014	Valia et al.
2014/0186332	A1	7/2014	Ezrin et al.
2014/0187487	A1	7/2014	Shoichet et al.
2014/0193523	A1	7/2014	Henry
2014/0194396	A1	7/2014	Li et al.
2014/0206616	A1	7/2014	Ko et al.

## FOREIGN PATENT DOCUMENTS

WO	WO03028667	4/2003
WO	WO2004014432	2/2004
WO	WO2005081825	9/2005
WO	WO2007120868	10/2007
WO	WO2010146872	12/2010
WO	WO2012055814	A1 5/2012
WO	WO2012055840	A1 5/2012
WO	WO2012065740	5/2012
WO	WO2012098090	A1 7/2012
WO	WO2012116277	A1 8/2012
WO	WO2012118563	A2 9/2012
WO	WO2012120365	A1 9/2012
WO	WO2012127501	A2 9/2012
WO	WO2012156561	A1 11/2012
WO	WO2012156822	A1 11/2012
WO	WO2012158483	A2 11/2012
WO	WO2012166909	A1 12/2012
WO	WO2012170578	A1 12/2012
WO	WO2013011501	A1 1/2013
WO	WO2013025449	A1 2/2013
WO	WO2013028639	A1 2/2013
WO	WO2013035101	A1 3/2013
WO	WO2013044067	A1 3/2013

WO	WO2013045404	A2 4/2013
WO	WO2013059285	A1 4/2013
WO	WO2013063279	A1 5/2013
WO	WO2013064620	A1 5/2013
WO	WO2013071281	A1 5/2013
WO	WO2013088254	6/2013
WO	WO2013102665	A1 7/2013
WO	WO2013106437	A1 7/2013
WO	WO2013113690	8/2013
WO	WO2013124415	A1 8/2013
WO	WO2013127727	A1 9/2013
WO	WO2013127728	A1 9/2013
WO	WO2013144356	A1 10/2013
WO	WO2013149258	A2 10/2013
WO	WO2013158454	A2 10/2013
WO	WO2013170052	A1 11/2013
WO	WO2013178587	A1 12/2013
WO	WO2014001904	A1 1/2014
WO	WO2014004424	A1 1/2014
WO	WO2014009434	A1 1/2014
WO	WO2014018569	A1 1/2014
WO	WO2014018570	A1 1/2014
WO	WO2014018571	A2 1/2014
WO	WO2014018856	A1 1/2014
WO	WO2014018932	A2 1/2014
WO	WO2014031958	A1 2/2014
WO	WO2014041120	A1 3/2014
WO	WO2014052792	A1 4/2014
WO	WO2014056897	A1 4/2014
WO	WO2014066442	A2 5/2014
WO	WO2014074846	A1 5/2014
WO	WO2014076231	A1 5/2014
WO	WO2014076569	A2 5/2014
WO	WO2014081598	A1 5/2014
WO	WO2014086739	A1 6/2014
WO	WO2014093114	A1 6/2014
WO	WO2014104784	A1 7/2014

## OTHER PUBLICATIONS

Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," *Clinical Pharmacy*, 1990, vol. 9, No. 5, pp. 366-371.

Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," *Journal of Pharmaceutical Sciences*, vol. 86, No. 1, Jan. 1997, pp. 13-18.

Sasol Olefins & Surfactants GmbH, *Excipients for Pharmaceuticals*, 2010, 28 pages.

Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," *Food and Chemical Toxicology*, 72 (2014) pp. 40-50.

Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," *Journal of Pharmaceutical Sciences*, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.

ZRT Laboratory, *Provider Data Sheet, About Dried Blood Spot Testing*, 2014, 3 pages.

\* cited by examiner

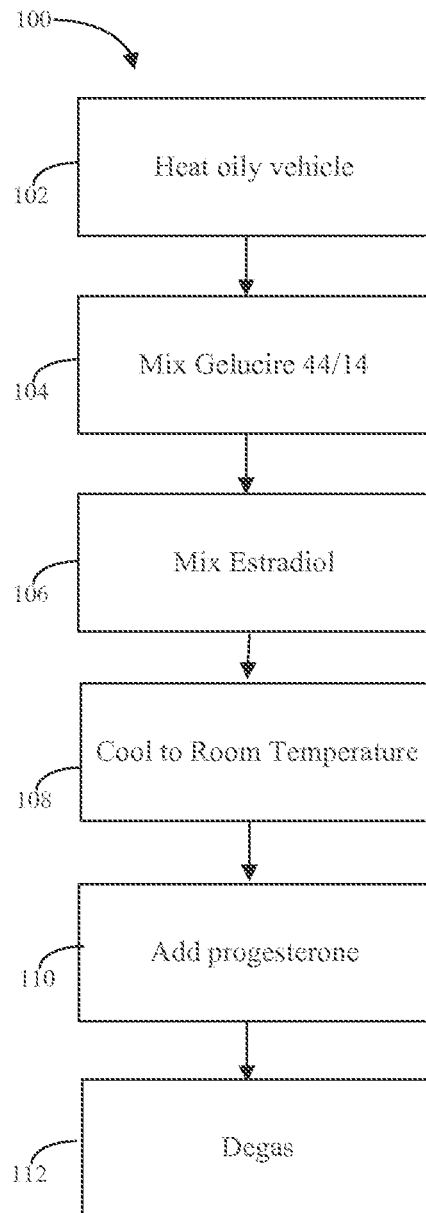
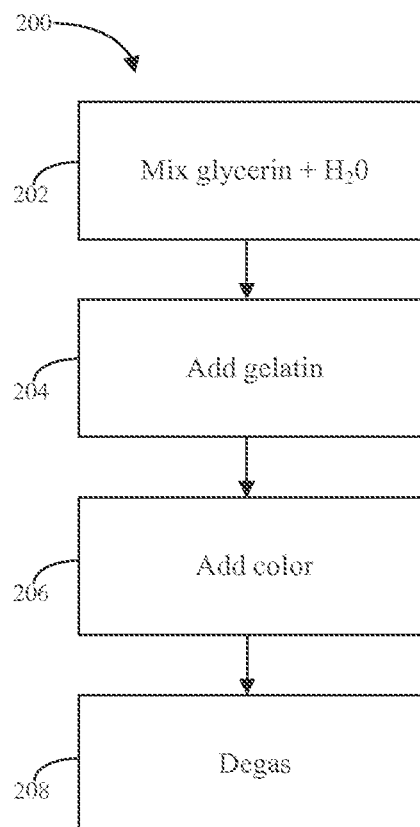


Fig. 1



**Fig. 2**

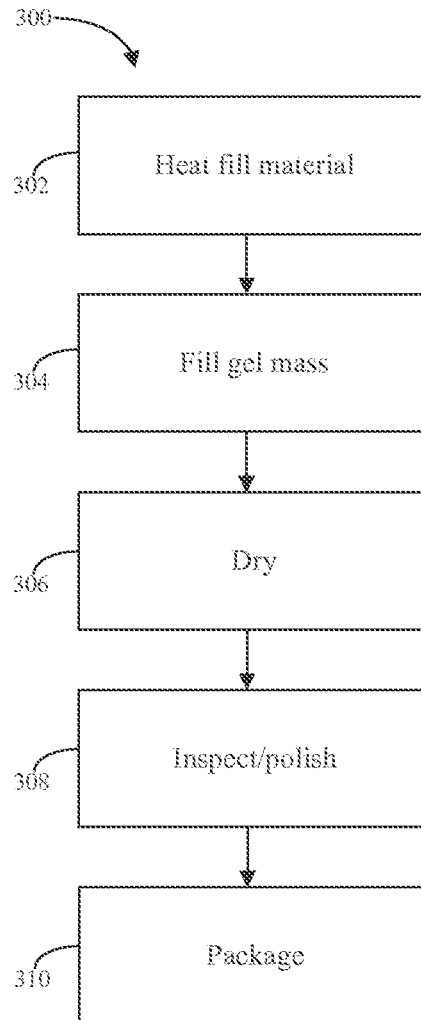


Fig. 3

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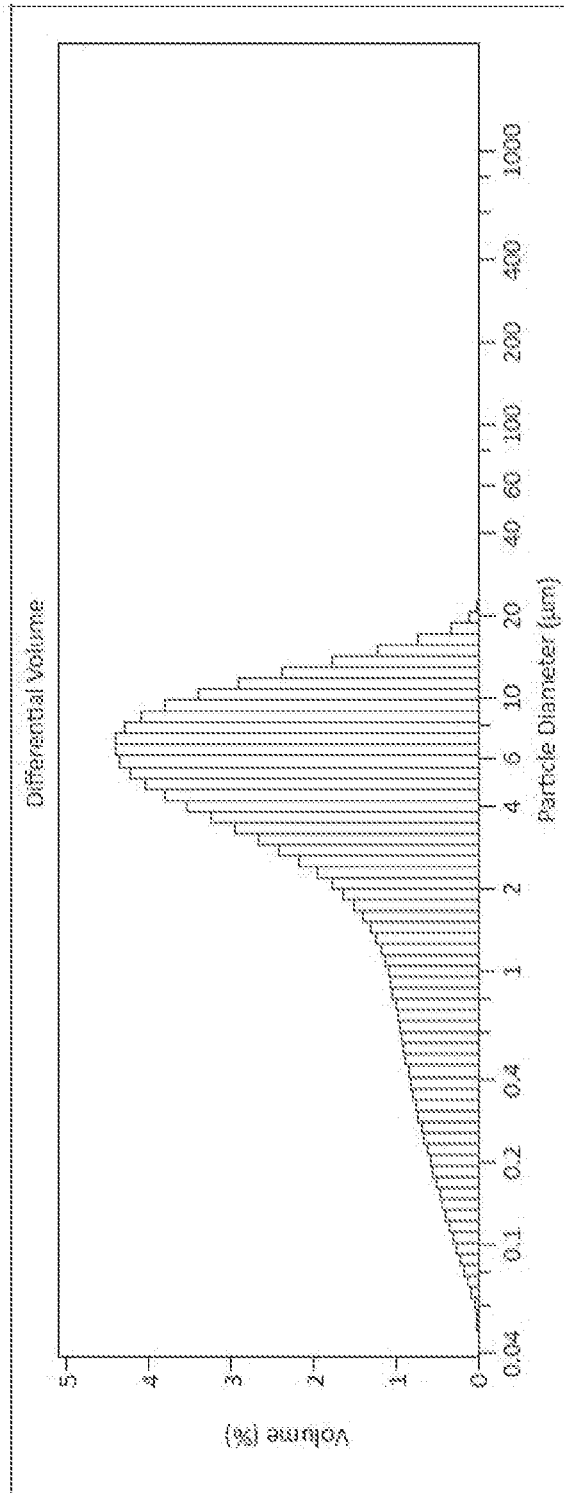


FIG. 4

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## NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

### CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/099,545, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Dec. 6, 2013, which application is a divisional of U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which application claims priority to the following U.S. Provisional patent applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

### FIELD OF THE INVENTION

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

### BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a

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constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

### SUMMARY OF THE INVENTION

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

### BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.



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## DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

## A. Definitions

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC,  $C_{max}$ , and optionally,  $T_{max}$ .

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, " $C_{max}$ " as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, " $T_{max}$ " as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC,  $C_{max}$  and, optionally,  $T_{max}$  are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating

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pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "oil" as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

"Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution.

"Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

## B. Description and Preferred Embodiments

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra-

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and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 $\beta$ -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125,

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1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017  $\mu$ m to 2000  $\mu$ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4  $\mu$ m to 2000  $\mu$ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

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Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol; Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Campul MCM; Capmul MCM and a non-ionic surfactant; and Campul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Campul MCM and Gelucire can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other

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solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2, 3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may

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contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

### EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

#### Example 1

##### Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and

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filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

\*Literature reference—Salole, E.G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

#### Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

#### Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.



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TABLE 3

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol:Miglyol:Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

## Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

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Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

## Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/ triglycerides of caprylic/ capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

## Example 7

## Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

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As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

## Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

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For example, Campul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/-2° C. Gelucire 44/14 may be added to the Campul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Campul MCM.

Heat may be removed from the Gelucire 44/14 and Campul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Campul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

## Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.



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## Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier

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with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0  $\mu\text{m}$ , an  $\times 75$  of 17.3  $\mu\text{m}$ , and an  $\times 25$  of 5.3  $\mu\text{m}$ . The Beckman Device also yielded that the mean particle size is 11.8  $\mu\text{m}$ , the median particle size is 11.04  $\mu\text{m}$ , the mode particle size is 13.6  $\mu\text{m}$ , and the standard deviation is 7.8  $\mu\text{m}$ .

## Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

TABLE 14-continued

Ingredient	%	mg/ Capsule	Function
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279  $\mu\text{m}$ , an  $\times 75$  of 7.442  $\mu\text{m}$ , and an  $\times 25$  of 1.590  $\mu\text{m}$ . The Beckman Device also yielded that the mean particle size is 4.975  $\mu\text{m}$ , the median particle size is 4.279  $\mu\text{m}$ , the mode particle size is 6.453  $\mu\text{m}$ , and the standard deviation is 3.956  $\mu\text{m}$ . A graph of the particle distribution obtained is shown in FIG. 4.

## Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

## Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:			100.000	200.00 mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

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TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 16

## Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout

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the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA-vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ± 20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

## Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ± 5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator,

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or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.±3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of

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FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.±10° C. The wedge temperature may be 38° C.±3° C. The drum cooling temperature may be 4° C.±2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant.

Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A pharmaceutical formulation comprising solubilized estradiol, suspended progesterone, and a medium chain solubilizing agent; wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and the suspended progesterone are uniformly dispersed; wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and wherein the solubilizing agent comprises an effective amount of a C6-C12 oil.

2. The pharmaceutical formulation of claim 1, further comprising partially solubilized progesterone.

3. The pharmaceutical formulation of claim 1, wherein the formulation is contained within a gelatin capsule.

4. The pharmaceutical formulation of claim 1, wherein the medium chain solubilizing agent is selected from at least one of mono-, di-, and triglycerides and combinations thereof.

5. The pharmaceutical formulation of claim 1, wherein said estradiol has a dosage strength at least about 0.125 mg and wherein said progesterone has a dosage strength at least about 25 mg.

6. The pharmaceutical formulation of claim 1, wherein the ratio of progesterone to estradiol is at least 95:1.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,993,548 B2  
APPLICATION NO. : 14/475814  
DATED : March 31, 2015  
INVENTOR(S) : Brian A. Bernick et al.

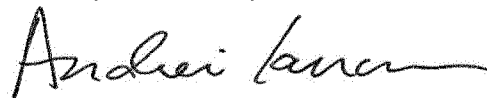
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this  
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu  
*Director of the United States Patent and Trademark Office*

# **EXHIBIT F**



US008993549B2

(12) **United States Patent**  
**Bernick et al.**

(10) **Patent No.:** **US 8,993,549 B2**  
(45) **Date of Patent:** **\*Mar. 31, 2015**

(54) **NATURAL COMBINATION HORMONE  
REPLACEMENT FORMULATIONS AND  
THERAPIES**

(56) **References Cited**

U.S. PATENT DOCUMENTS

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(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.  
  
This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/475,864**

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**Related U.S. Application Data**

(63) Continuation of application No. 14/099,571, filed on Dec. 6, 2013, now Pat. No. 8,846,649, which is a continuation of application No. 13/684,002, filed on Nov. 21, 2012, now Pat. No. 8,633,178.

(60) Provisional application No. 61/662,265, filed on Jun. 20, 2012, provisional application No. 61/661,302, filed on Jun. 18, 2012, provisional application No. 61/563,408, filed on Nov. 23, 2011.

(51) **Int. Cl.**

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**A61K 9/48** (2006.01)  
**A61K 31/57** (2006.01)  
**A61K 9/16** (2006.01)  
**A61K 31/565** (2006.01)  
**A61K 9/70** (2006.01)

(52) **U.S. Cl.**

CPC . **A61K 31/57** (2013.01); **A61K 9/16** (2013.01);  
**A61K 31/565** (2013.01); **A61K 9/4858**  
(2013.01); **A61K 9/7023** (2013.01)  
USPC ..... **514/169**; 424/452

(58) **Field of Classification Search**

CPC ..... **A61K 31/57**; **A61K 31/565**  
USPC ..... **514/169**; 424/452  
See application file for complete search history.

2,232,438 A	2/1941	Butenandt	
4,900,734 A *	2/1990	Maxson et al.	..... 514/171
5,538,736 A	7/1996	Barth et al.	
5,556,635 A	9/1996	Grognet et al.	
5,580,572 A	12/1996	Liorzou et al.	
5,605,702 A	2/1997	Math et al.	
5,607,691 A	3/1997	Solas et al.	
5,607,693 A	3/1997	Bonte et al.	
5,609,617 A	3/1997	Cady et al.	
5,626,866 A	5/1997	Heiber et al.	
5,653,983 A	8/1997	Bonte et al.	
5,660,839 A	8/1997	Allec et al.	
5,662,927 A	9/1997	Ehrlich et al.	
5,663,160 A	9/1997	Dumas et al.	
5,686,097 A	11/1997	Crisologo et al.	
5,693,335 A	12/1997	Xia et al.	
5,700,480 A	12/1997	Hille et al.	
5,719,197 A	2/1998	Mantelle et al.	
5,770,220 A	6/1998	Meconi et al.	
5,770,227 A	6/1998	Dong et al.	
5,780,044 A	7/1998	Tipton et al.	
5,780,050 A	7/1998	Jain et al.	
5,788,984 A	8/1998	Schmidt et al.	
5,820,878 A	10/1998	Shinmura et al.	
5,840,327 A	11/1998	Gale et al.	
5,843,468 A	12/1998	Yum et al.	
5,843,979 A	12/1998	Wille et al.	
5,858,394 A	1/1999	Lipp et al.	
5,863,552 A	1/1999	Yue	

(Continued)

FOREIGN PATENT DOCUMENTS

WO	WO9619975	7/1996
WO	WO0241878	5/2002

(Continued)

OTHER PUBLICATIONS

Abitec Corporation, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.

(Continued)

*Primary Examiner* — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton LLP

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

**18 Claims, 4 Drawing Sheets**



## US 8,993,549 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

5,882,676	A	3/1999	Yum et al.	7,094,228	B2	8/2006	Zhang et al.
5,885,612	A	3/1999	Meconi et al.	7,097,853	B1	8/2006	Keister et al.
5,888,533	A	3/1999	Dunn	7,105,573	B2	9/2006	Krajcik et al.
5,891,462	A	4/1999	Carrara	7,153,522	B1	12/2006	Ikeura et al.
5,902,603	A	5/1999	Chen et al.	7,175,850	B2	2/2007	Cevc
5,904,931	A	5/1999	Gunther et al.	7,198,800	B1	4/2007	Ko
5,906,830	A	5/1999	Farinas et al.	7,381,427	B2	6/2008	Ancira et al.
5,912,010	A	6/1999	Wille et al.	7,456,159	B2	11/2008	Houze et al.
5,919,477	A	7/1999	Bevan et al.	7,498,303	B2	3/2009	Arnold et al.
5,942,243	A	8/1999	Shah	7,534,780	B2	5/2009	Ring et al.
5,952,000	A	9/1999	Fikstad et al.	7,569,274	B2	8/2009	Alphonse et al.
5,968,919	A	10/1999	Gyurik et al.	7,799,769	B2	9/2010	White et al.
5,985,311	A	11/1999	Cordes et al.	7,815,936	B2	10/2010	Hasenzahl et al.
5,985,850	A	11/1999	Falk et al.	7,829,116	B2	11/2010	Frye et al.
5,989,568	A	11/1999	De Lacharriere et al.	7,850,992	B2	12/2010	Hwang, II et al.
6,007,835	A	12/1999	Bon Lapillonne et al.	7,854,753	B2	12/2010	Kraft et al.
6,010,715	A	1/2000	Pollock et al.	7,871,643	B2	1/2011	Lizio et al.
6,013,276	A	1/2000	Teillaud et al.	7,960,368	B2	6/2011	Rao et al.
6,024,974	A	2/2000	Li	8,048,017	B2	11/2011	Xu
6,030,948	A	2/2000	Mann	8,063,030	B2	11/2011	Ellman
6,040,340	A	3/2000	Garfield et al.	8,071,576	B2	12/2011	Visser et al.
6,068,853	A	5/2000	Berner et al.	8,075,916	B2	12/2011	Park et al.
6,087,352	A	7/2000	Trout	8,075,917	B2	12/2011	Park et al.
6,090,404	A	7/2000	Meconi et al.	8,076,317	B2	12/2011	Kulmann
6,106,848	A	8/2000	Willcox et al.	8,080,553	B2	12/2011	Auspitz et al.
6,124,362	A	9/2000	Bradbury et al.	8,096,940	B2	1/2012	Iverson et al.
6,139,868	A	10/2000	Hoffmann	8,114,152	B2	2/2012	Furst
6,149,935	A	11/2000	Tenzel et al.	8,114,442	B2	2/2012	Tucker et al.
6,187,323	B1	2/2001	Aiache et al.	8,119,741	B2	2/2012	Pavlin
6,217,886	B1	4/2001	Rubinstein et al.	8,124,118	B2	2/2012	Lennernaes et al.
6,225,297	B1	5/2001	Stockemann et al.	8,124,595	B2	2/2012	Boissonneault
6,228,383	B1	5/2001	Hansen et al.	8,147,561	B2	4/2012	Binmoeller
6,228,852	B1	5/2001	Shaak	8,148,546	B2	4/2012	Baasner et al.
6,242,509	B1	6/2001	MacQueen et al.	8,158,613	B2	4/2012	Staniforth et al.
6,245,811	B1	6/2001	Horrobin et al.	8,163,722	B2	4/2012	Savoir et al.
6,267,984	B1	7/2001	Hamlin et al.	8,177,449	B2	5/2012	Watkinson et al.
6,274,165	B1	8/2001	Meconi et al.	8,187,615	B2	5/2012	Friedman
6,303,132	B1	10/2001	Nelson	8,195,403	B2	6/2012	Wood, Jr. et al.
6,303,588	B1	10/2001	Danielov	8,221,785	B2	7/2012	Chien
6,312,703	B1	11/2001	Orthoefer	8,222,237	B2	7/2012	Narkunan et al.
6,328,987	B1	12/2001	Marini	8,257,724	B2	9/2012	Cromack et al.
6,344,211	B1	2/2002	Hille et al.	8,257,725	B2	9/2012	Cromack et al.
6,372,245	B1	4/2002	Vo et al.	8,268,352	B2	9/2012	Karan et al.
6,420,352	B1	7/2002	Knowles	8,268,806	B2	9/2012	Labrie
6,432,438	B1	8/2002	Shukla	8,268,878	B2	9/2012	Armer et al.
6,451,300	B1	9/2002	Leyba et al.	8,288,366	B2	10/2012	Gonzalez et al.
6,465,004	B1	10/2002	Houze et al.	8,318,898	B2	11/2012	Fasel et al.
6,465,005	B1	10/2002	Biali et al.	8,324,193	B2	12/2012	Lee et al.
6,465,006	B1	10/2002	Zhang et al.	8,337,814	B2	12/2012	Osbakken et al.
6,495,160	B2	12/2002	Esposito et al.	8,344,007	B2	1/2013	Chui et al.
6,521,250	B2	2/2003	Seibert et al.	8,353,863	B2	1/2013	Imran
6,531,149	B1	3/2003	Meconi et al.	8,357,723	B2	1/2013	Satyam
6,538,039	B2	3/2003	Laurent	8,361,995	B2	1/2013	Schramm
6,548,053	B1	4/2003	Murray et al.	8,362,091	B2	1/2013	Besonov et al.
6,555,131	B1	4/2003	Wolff et al.	8,372,424	B2	2/2013	Berry et al.
6,562,367	B1	5/2003	Wolff et al.	8,372,806	B2	2/2013	Bragagna et al.
6,562,370	B2	5/2003	Luo et al.	8,377,482	B2	2/2013	Laurie et al.
6,562,790	B2	5/2003	Chein	8,377,994	B2	2/2013	Drechsler et al.
6,599,519	B1	7/2003	Seo et al.	8,394,759	B2	3/2013	Barathur et al.
6,610,674	B1	8/2003	Schreiber	8,415,332	B2	4/2013	Reape et al.
6,635,274	B1	10/2003	Carter et al.	8,435,972	B2	5/2013	Sayeed et al.
6,638,528	B1	10/2003	Kanios	8,449,879	B2	5/2013	Laurent et al.
6,649,155	B1	11/2003	Dunlop et al.	8,450,108	B2	5/2013	Boyce
6,682,757	B1	1/2004	Wright	8,454,945	B2	6/2013	Narain et al.
6,708,822	B1	3/2004	Muni	8,455,468	B2	6/2013	Kellerman et al.
6,720,001	B2	4/2004	Chen et al.	8,461,138	B2	6/2013	Boissonneault
6,743,448	B2	6/2004	Kryger	8,476,252	B2	7/2013	Pickersgill et al.
6,750,291	B2	6/2004	Kim et al.	8,481,488	B2	7/2013	Carter
6,821,524	B2	11/2004	Marini	8,486,374	B2	7/2013	Zlatkis et al.
6,911,211	B2	6/2005	Tamarkin et al.	8,486,442	B2	7/2013	Yamaji et al.
6,960,337	B2	11/2005	Pike et al.	8,492,368	B2	7/2013	Lewandowski et al.
6,974,569	B2	12/2005	Boyd et al.	8,507,467	B2	8/2013	Ueda et al.
6,995,149	B1	2/2006	Reilhac et al.	8,512,693	B2	8/2013	Azevedo et al.
7,004,321	B1	2/2006	Hackbarth et al.	8,512,754	B2	8/2013	Needham
7,030,104	B2	4/2006	Paris et al.	8,518,376	B2	8/2013	Schuz et al.
				8,536,159	B2	9/2013	Zeng et al.
				8,540,967	B2	9/2013	Trivedi et al.
				8,541,400	B2	9/2013	Joabsson et al.
				8,551,462	B2	10/2013	Marenus et al.

## US 8,993,549 B2

Page 3

(56)

## References Cited

## U.S. PATENT DOCUMENTS

8,557,281	B2	10/2013	Tuominen et al.	2005/0186141	A1	8/2005	Gonda et al.
8,568,374	B2	10/2013	De Graaff et al.	2005/0196434	A1	9/2005	Brierre
8,591,951	B2	11/2013	Kohn et al.	2005/0220900	A1	10/2005	Wuttke et al.
8,613,951	B2	12/2013	Troiano et al.	2005/0239747	A1	10/2005	Le et al.
8,633,178	B2	1/2014	Cacace et al.	2005/0239758	A1	10/2005	Roby
8,633,180	B2	1/2014	Zeng et al.	2005/0244360	A1	11/2005	Billoni
8,636,787	B2	1/2014	Sabaria	2005/0266088	A1	12/2005	Frijlink et al.
8,636,982	B2	1/2014	Schuz et al.	2005/0271597	A1	12/2005	Keith
8,653,129	B2	2/2014	Fein et al.	2005/0272685	A1	12/2005	Hung
8,658,627	B2	2/2014	Voskuhl	2006/0009428	A1	1/2006	Grubb et al.
8,663,692	B1	3/2014	Mueller et al.	2006/0034904	A1	2/2006	Weimann
8,663,703	B2	3/2014	Moldavski et al.	2006/0078618	A1	4/2006	Constantinides et al.
8,664,207	B2	3/2014	Zheng et al.	2006/0084704	A1	4/2006	Shih et al.
8,669,293	B2	3/2014	Sharoni et al.	2006/0088580	A1	4/2006	Seibert et al.
8,679,552	B2	3/2014	Guthery	2006/0100180	A1	5/2006	Bohlmann et al.
8,697,127	B2	4/2014	Sah	2006/0121102	A1	6/2006	Chiang
8,697,710	B2	4/2014	Zeng et al.	2006/0165744	A1	7/2006	Anyarambhatla et al.
8,703,105	B2	4/2014	Besonov et al.	2006/0193789	A1	8/2006	Tamarkin et al.
8,709,385	B2	4/2014	Schuz et al.	2006/0233743	A1	10/2006	Kelly
8,709,451	B2	4/2014	Rapoport et al.	2006/0233841	A1	10/2006	Pushpala et al.
8,715,735	B2	5/2014	Funke et al.	2006/0246122	A1	11/2006	Langguth et al.
8,721,331	B2	5/2014	Raghuprasad	2006/0247221	A1	11/2006	Coelingh et al.
8,722,021	B2	5/2014	Eini et al.	2006/0251581	A1	11/2006	Madenjian et al.
8,734,846	B2	5/2014	Hrkach et al.	2006/0275218	A1	12/2006	Besonov et al.
8,735,381	B2	5/2014	Podolski	2006/0276414	A1	12/2006	Coelingh et al.
8,741,336	B2	6/2014	Dipierro et al.	2006/0292223	A1	12/2006	Mc Ilroy et al.
8,741,373	B2	6/2014	Rao et al.	2007/0009559	A1	1/2007	Alosio et al.
8,753,661	B2	6/2014	Gassner et al.	2007/0009594	A1	1/2007	Grubb et al.
8,784,882	B2	7/2014	Mattern	2007/0010550	A1	1/2007	McKenzie
2001/0009673	A1	7/2001	Gunther et al.	2007/0014839	A1	1/2007	Bracht
2001/0023261	A1	9/2001	Ryoo et al.	2007/0015698	A1	1/2007	Goldstein et al.
2001/0053383	A1	12/2001	Sablotsky et al.	2007/0037780	A1	2/2007	Anigbogu et al.
2002/0035070	A1	3/2002	Gardlik et al.	2007/0037782	A1	2/2007	Suzuki et al.
2002/0119174	A1	8/2002	Gardlik et al.	2007/0078091	A1	4/2007	Hubler et al.
2002/0119198	A1	8/2002	Gao et al.	2007/0128263	A1	6/2007	Wall et al.
2002/0142017	A1	10/2002	Simonnet	2007/0154533	A1	7/2007	Dudley
2002/0169205	A1	11/2002	Garfield et al.	2007/0167418	A1	7/2007	Ferguson
2002/0193758	A1	12/2002	Sandberg	2007/0185068	A1	8/2007	Ferguson et al.
2002/0197286	A1	12/2002	Brandman et al.	2007/0190022	A1	8/2007	Chiao et al.
2003/0003139	A1	1/2003	Gunther et al.	2007/0196415	A1	8/2007	Houston et al.
2003/0027772	A1	2/2003	Breton	2007/0232574	A1	10/2007	Bernard et al.
2003/0044453	A1	3/2003	Volkel et al.	2007/0248658	A1	10/2007	Bracht et al.
2003/0091620	A1	5/2003	Venkateshwaran et al.	2007/0254858	A1	11/2007	Cronk
2003/0109507	A1	6/2003	Beckmann et al.	2007/0255197	A1	11/2007	Wilkins et al.
2003/0113268	A1	6/2003	Buenafae et al.	2007/0287688	A1	12/2007	Chan et al.
2003/0170295	A1	9/2003	Yoon et al.	2007/0292359	A1	12/2007	Schuz et al.
2003/0175329	A1	9/2003	Mak et al.	2007/0292461	A1	12/2007	Danziger et al.
2003/0175333	A1	9/2003	Shefer et al.	2007/0292493	A1	12/2007	Brierre
2003/0219402	A1	11/2003	Rutter	2007/0298089	A1	12/2007	Yoshinaga et al.
2003/0225047	A1	12/2003	Friedman et al.	2008/0026040	A1	1/2008	Rivera et al.
2003/0225048	A1	12/2003	Friedman et al.	2008/0038219	A1	2/2008	Carlson et al.
2003/0235596	A1	12/2003	Gao et al.	2008/0039405	A1	2/2008	Joseph et al.
2003/0236236	A1	12/2003	Chen et al.	2008/0050317	A1	2/2008	Besonov et al.
2004/0022820	A1	2/2004	Anderson	2008/0051351	A1	2/2008	Ghisalberti
2004/0039356	A1	2/2004	Maki et al.	2008/0063607	A1	3/2008	Berman et al.
2004/0043043	A1	3/2004	Schlyter et al.	2008/0069779	A1	3/2008	Schuz et al.
2004/0048900	A1	3/2004	Flood	2008/0069791	A1	3/2008	Beissert
2004/0087564	A1	5/2004	Wright et al.	2008/0095831	A1	4/2008	Mc Graw
2004/0092494	A9	5/2004	Dudley	2008/0138390	A1	6/2008	Gricenko et al.
2004/0110732	A1	6/2004	Masini et al.	2008/0139392	A1	6/2008	Yuan et al.
2004/0138103	A1	7/2004	Patt	2008/0153789	A1	6/2008	Dmowski et al.
2004/0146539	A1	7/2004	Gupta	2008/0175905	A1	7/2008	Baksh et al.
2004/0161435	A1	8/2004	Gupta	2008/0175908	A1	7/2008	Baksh et al.
2004/0191207	A1	9/2004	Lipari et al.	2008/0206156	A1	8/2008	Cronk
2004/0210280	A1	10/2004	Liedtke	2008/0206159	A1	8/2008	Schuz et al.
2004/0219124	A1	11/2004	Gupta	2008/0214512	A1	9/2008	Seitz et al.
2004/0225140	A1	11/2004	Sciano et al.	2008/0226698	A1	9/2008	Beste et al.
2004/0241219	A1	12/2004	Hille et al.	2008/0227763	A1	9/2008	Paris et al.
2005/0003003	A1	1/2005	Deaver et al.	2008/0234240	A1	9/2008	Duesterberg et al.
2005/0014729	A1	1/2005	Pulaski	2008/0261931	A1	10/2008	Stenlof et al.
2005/0020550	A1	1/2005	Latif et al.	2009/0004246	A1	1/2009	Woolfson et al.
2005/0054991	A1	3/2005	Paterson et al.	2009/0010968	A1	1/2009	Peyrot et al.
2005/0118244	A1	6/2005	Theobald et al.	2009/0011041	A1	1/2009	Musaeva et al.
2005/0129756	A1	6/2005	Podhaisky et al.	2009/0017120	A1	1/2009	Brisco et al.
2005/0152956	A1	7/2005	Dudley	2009/0022683	A1	1/2009	Park et al.
				2009/0047357	A1	2/2009	Tomohira et al.
				2009/0060997	A1	3/2009	Seitz et al.
				2009/0081206	A1	3/2009	Leibovitz
				2009/0093440	A1	4/2009	Murad

## US 8,993,549 B2

Page 4

## (56) References Cited

## U.S. PATENT DOCUMENTS

2009/0098069	A1	4/2009	Vacca	2012/0129773	A1	5/2012	Geier et al.
2009/0099149	A1	4/2009	Kresevic et al.	2012/0129819	A1	5/2012	Vancaillie et al.
2009/0130029	A1	5/2009	Tamarkin et al.	2012/0136013	A1	5/2012	Wennogle et al.
2009/0175799	A1	7/2009	Tamarkin et al.	2012/0142645	A1	6/2012	Marx
2009/0186081	A1	7/2009	Slot et al.	2012/0148670	A1	6/2012	Lee et al.
2009/0197843	A1	8/2009	Notelovitz et al.	2012/0172343	A1	7/2012	Schuermann et al.
2009/0203658	A1	8/2009	Rose et al.	2012/0184515	A1	7/2012	Schwede et al.
2009/0227550	A1	9/2009	Mattern	2012/0231052	A1	9/2012	Brinton et al.
2009/0285869	A1	11/2009	Trimble	2012/0232011	A1	9/2012	Kneissel et al.
2009/0324714	A1	12/2009	Kresevic et al.	2012/0232042	A1	9/2012	Krenz et al.
2010/0008985	A1	1/2010	Vermeulen et al.	2012/0263679	A1	10/2012	Wallace et al.
2010/0034838	A1	2/2010	Staniforth et al.	2012/0277249	A1	11/2012	Tarrand et al.
2010/0034880	A1	2/2010	Sintov et al.	2012/0277727	A1	11/2012	Doshi et al.
2010/0055138	A1	3/2010	Jacobs et al.	2012/0295911	A1	11/2012	Mannion et al.
2010/0086501	A1	4/2010	Chang et al.	2012/0301517	A1	11/2012	Warner et al.
2010/0119585	A1	5/2010	Hille et al.	2012/0301538	A1	11/2012	Latere et al.
2010/0143420	A1	6/2010	Lee et al.	2012/0302535	A1	11/2012	Caufriez et al.
2010/0143481	A1	6/2010	Shenoy et al.	2012/0316130	A1	12/2012	Hendrix
2010/0150993	A1	6/2010	Theobald et al.	2012/0316496	A1	12/2012	Horres et al.
2010/0204326	A1	8/2010	D'Souza	2012/0321579	A1	12/2012	Edelson et al.
2010/0210994	A1	8/2010	Zarif	2012/0322779	A9	12/2012	Voskuhl
2010/0221195	A1	9/2010	Ziv et al.	2012/0328549	A1	12/2012	Edelson et al.
2010/0227797	A1	9/2010	Danielsson et al.	2012/0329738	A1	12/2012	Liu
2010/0247482	A1	9/2010	Chen et al.	2013/0004619	A1	1/2013	Goh et al.
2010/0247635	A1	9/2010	Schmidt et al.	2013/0011342	A1	1/2013	Hazot et al.
2010/0273730	A1	10/2010	Hsu et al.	2013/0017239	A1	1/2013	Fernandez et al.
2010/0278759	A1	11/2010	Murad	2013/0023505	A1	1/2013	Garfield et al.
2010/0279988	A1	11/2010	Setiawan et al.	2013/0023823	A1	1/2013	Volland et al.
2010/0291191	A1	11/2010	Lapitsky et al.	2013/0028850	A1	1/2013	Hazot et al.
2010/0292199	A1	11/2010	Leverd et al.	2013/0029957	A1	1/2013	Venkateshwaran et al.
2010/0322884	A1	12/2010	Wilkins et al.	2013/0045266	A1	2/2013	Kang et al.
2011/0039814	A1	2/2011	Ross et al.	2013/0045953	A1	2/2013	Grenier et al.
2011/0087192	A1	4/2011	Uhland et al.	2013/0059795	A1	3/2013	Lo et al.
2011/0098258	A1	4/2011	Canet et al.	2013/0064897	A1	3/2013	Binay
2011/0104268	A1	5/2011	Segot et al.	2013/0072466	A1	3/2013	Choi et al.
2011/0130372	A1	6/2011	Marliani et al.	2013/0084257	A1	4/2013	Ishida et al.
2011/0142945	A1	6/2011	Chen et al.	2013/0085123	A1	4/2013	Zhao et al.
2011/0152840	A1	6/2011	Lee et al.	2013/0089574	A1	4/2013	Stock et al.
2011/0158920	A1	6/2011	Fisher et al.	2013/0090318	A1	4/2013	Gainer et al.
2011/0171140	A1	7/2011	Illum et al.	2013/0102781	A1	4/2013	Ely et al.
2011/0190201	A1	8/2011	Wood, Jr. et al.	2013/0108551	A1	5/2013	Gruell et al.
2011/0195031	A1	8/2011	Du	2013/0116215	A1	5/2013	Lleo et al.
2011/0238003	A1	9/2011	Karabelas et al.	2013/0116222	A1	5/2013	Altomari et al.
2011/0244043	A1	10/2011	Wang et al.	2013/0122051	A1	5/2013	Gullapalli et al.
2011/0250256	A1	10/2011	Hyun et al.	2013/0123175	A1	5/2013	McKee et al.
2011/0250259	A1	10/2011	Buckman	2013/0123220	A1	5/2013	Queiroz
2011/0262373	A1	10/2011	Umbert	2013/0123351	A1	5/2013	Dewitt
2011/0275584	A1	11/2011	Volkman et al.	2013/0131027	A1	5/2013	Schmitz et al.
2011/0281832	A1	11/2011	Wennogle et al.	2013/0131028	A1	5/2013	Snyder et al.
2011/0287094	A1	11/2011	Penhasi et al.	2013/0131029	A1	5/2013	Baltussen et al.
2011/0294738	A1	12/2011	Kuliopulos et al.	2013/0149314	A1	6/2013	Bullerdiek et al.
2011/0300167	A1	12/2011	Covic et al.	2013/0164225	A1	6/2013	Besonov et al.
2011/0301087	A1	12/2011	McBride et al.	2013/0164346	A1	6/2013	Son et al.
2011/0306579	A1	12/2011	Stein	2013/0165744	A1	6/2013	Carson et al.
2011/0318405	A1	12/2011	Erwin	2013/0178452	A1	7/2013	King
2011/0318431	A1	12/2011	Gulati	2013/0183254	A1	7/2013	Cochran et al.
2012/0021041	A1	1/2012	Rossi et al.	2013/0183325	A1	7/2013	Sforzini et al.
2012/0028888	A1	2/2012	Janz et al.	2013/0189193	A1	7/2013	Besonov et al.
2012/0028910	A1	2/2012	Takruri et al.	2013/0189196	A1	7/2013	Tamarkin et al.
2012/0028936	A1	2/2012	Popova et al.	2013/0189230	A1	7/2013	Kooy et al.
2012/0046264	A1	2/2012	Lieb et al.	2013/0189368	A1	7/2013	Mosqueira et al.
2012/0046518	A1	2/2012	Yoakum et al.	2013/0210709	A1	8/2013	Covic et al.
2012/0058171	A1	3/2012	Zeeman et al.	2013/0216550	A1	8/2013	Penninger et al.
2012/0058962	A1	3/2012	Sparrow et al.	2013/0216596	A1	8/2013	Fernandez et al.
2012/0058979	A1	3/2012	Auspitz et al.	2013/0224177	A1	8/2013	Kim et al.
2012/0064135	A1	3/2012	Harms et al.	2013/0224257	A1	8/2013	Sah et al.
2012/0065179	A1	3/2012	Andersson	2013/0224268	A1	8/2013	Jaikaria et al.
2012/0087872	A1	4/2012	Schuz et al.	2013/0224300	A1	8/2013	Maggio
2012/0101073	A1	4/2012	Mannion et al.	2013/0225412	A1	8/2013	Sardari Lodriche et al.
2012/0121517	A1	5/2012	Kim et al.	2013/0225542	A1	8/2013	Frick et al.
2012/0121692	A1	5/2012	Fang et al.	2013/0226113	A1	8/2013	Langguth et al.
2012/0122829	A1	5/2012	Masini et al.	2013/0243696	A1	9/2013	Wang et al.
2012/0128654	A1	5/2012	Terpstra et al.	2013/0245253	A1	9/2013	Mook et al.
2012/0128683	A1	5/2012	Shantha	2013/0245570	A1	9/2013	Jackson
2012/0128733	A1	5/2012	Perrin et al.	2013/0261096	A1	10/2013	Merian et al.
				2013/0266645	A1	10/2013	Schoenecker et al.
				2013/0267485	A1	10/2013	Da Silva
				2013/0273167	A1	10/2013	Kim et al.
				2013/0274211	A1	10/2013	Prusthy et al.

## US 8,993,549 B2

Page 5

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2013/0280213 A1 10/2013 Voskuhl  
 2013/0316374 A1 11/2013 Menon et al.  
 2013/0317065 A1 11/2013 Seto et al.  
 2013/0317315 A1 11/2013 Tsang et al.  
 2013/0324565 A1 12/2013 Zhao et al.  
 2013/0331363 A1 12/2013 Zhao et al.  
 2013/0338124 A1 12/2013 Zhao et al.  
 2013/0345187 A1 12/2013 Rodriguez  
 2014/0018335 A1 1/2014 Seto et al.  
 2014/0024590 A1 1/2014 Taylor et al.  
 2014/0031289 A1 1/2014 Kim et al.  
 2014/0031323 A1 1/2014 Perez  
 2014/0066416 A1 3/2014 Leunis et al.  
 2014/0072531 A1 3/2014 Oh et al.  
 2014/0079686 A1 3/2014 Prouty et al.  
 2014/0088058 A1 3/2014 Maurizio  
 2014/0088059 A1 3/2014 Santha et al.  
 2014/0094426 A1 4/2014 Drummond et al.  
 2014/0100159 A1 4/2014 Conrad  
 2014/0100206 A1 4/2014 Cacace et al.  
 2014/0113889 A1 4/2014 Haine et al.  
 2014/0127185 A1 5/2014 Sayeed et al.  
 2014/0127280 A1 5/2014 Jukarainen et al.  
 2014/0127308 A1 5/2014 Opara et al.  
 2014/0128798 A1 5/2014 Malanchin et al.  
 2014/0148491 A1 5/2014 Valia et al.  
 2014/0186332 A1 7/2014 Ezrin et al.  
 2014/0187487 A1 7/2014 Shoichet et al.  
 2014/0193523 A1 7/2014 Henry  
 2014/0194396 A1 7/2014 Wennogle et al.  
 2014/0206616 A1 7/2014 Ko et al.

## FOREIGN PATENT DOCUMENTS

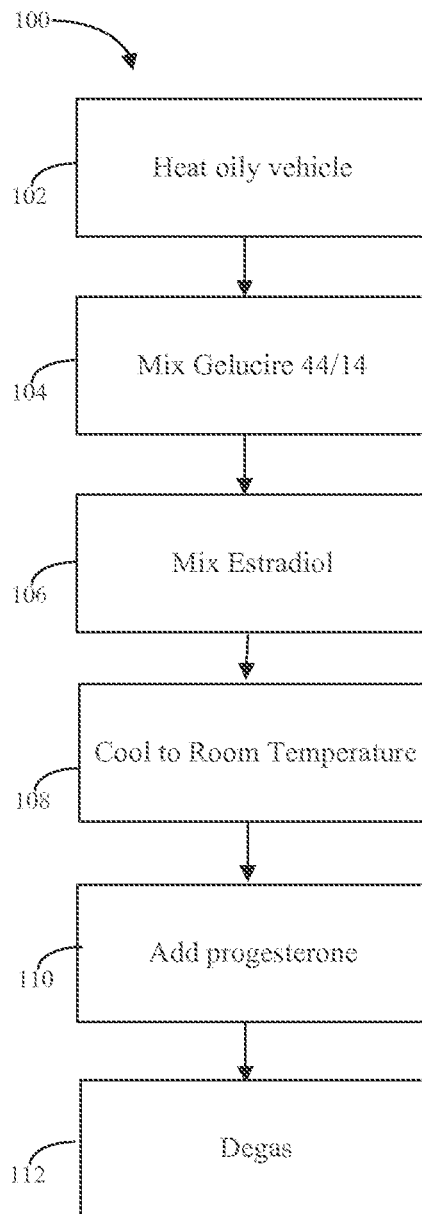
WO WO03028667 4/2003  
 WO WO2004014432 2/2004  
 WO WO2005081825 9/2005  
 WO WO2007120868 10/2007  
 WO WO2010146872 12/2010  
 WO WO2012055814 A1 5/2012  
 WO WO2012055840 A1 5/2012  
 WO WO2012065740 5/2012  
 WO WO2012098090 A1 7/2012  
 WO WO2012116277 A1 8/2012  
 WO WO2012118563 A2 9/2012  
 WO WO2012120365 A1 9/2012  
 WO WO2012127501 A2 9/2012  
 WO WO2012156561 A1 11/2012  
 WO WO2012156822 A1 11/2012  
 WO WO2012156822 A2 11/2012  
 WO WO2012158483 A2 11/2012  
 WO WO2012166909 A1 12/2012  
 WO WO2012170578 A1 12/2012  
 WO WO2013011501 A1 1/2013  
 WO WO2013025449 A1 2/2013  
 WO WO2013028639 A1 2/2013  
 WO WO2013035101 A1 3/2013  
 WO WO2013044067 A1 3/2013  
 WO WO2013045404 A2 4/2013  
 WO WO2013059285 A1 4/2013  
 WO WO2013063279 A1 5/2013  
 WO WO2013064620 A1 5/2013  
 WO WO2013071281 A1 5/2013  
 WO WO2013088254 6/2013

WO WO2013102665 A1 7/2013  
 WO WO2013102665 A1 7/2013  
 WO WO2013106437 A1 7/2013  
 WO WO2013113690 8/2013  
 WO WO2013124415 A1 8/2013  
 WO WO2013127727 A1 9/2013  
 WO WO2013127728 A1 9/2013  
 WO WO2013144356 A1 10/2013  
 WO WO2013149258 A2 10/2013  
 WO WO2013158454 A2 10/2013  
 WO WO2013170052 A1 11/2013  
 WO WO2013178587 A1 12/2013  
 WO WO2013181449 A1 12/2013  
 WO WO2014001904 A1 1/2014  
 WO WO2014004424 A1 1/2014  
 WO WO2014009434 A1 1/2014  
 WO WO2014018569 A1 1/2014  
 WO WO2014018570 A1 1/2014  
 WO WO2014018571 A2 1/2014  
 WO WO2014018856 A1 1/2014  
 WO WO2014018932 A2 1/2014  
 WO WO2014031958 A1 2/2014  
 WO WO2014041120 A1 3/2014  
 WO WO2014052792 A1 4/2014  
 WO WO2014056897 A1 4/2014  
 WO WO2014066442 A2 5/2014  
 WO WO2014074846 A1 5/2014  
 WO WO2014076231 A1 5/2014  
 WO WO2014076569 A2 5/2014  
 WO WO2014081598 A1 5/2014  
 WO WO2014086739 A1 6/2014  
 WO WO2014093114 A1 6/2014  
 WO WO2014104784 A1 7/2014

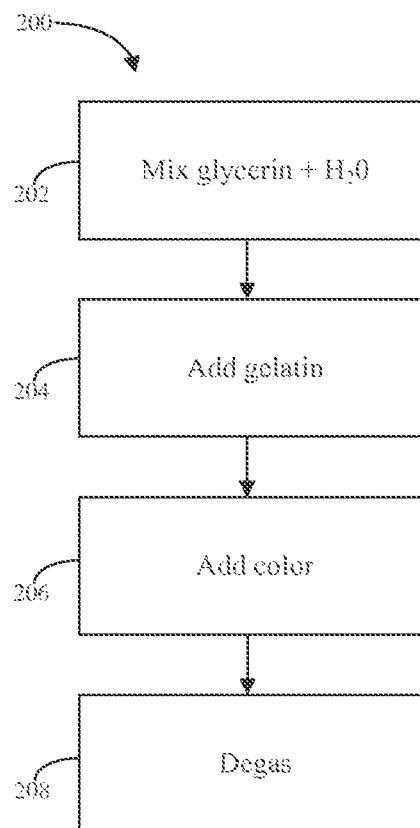
## OTHER PUBLICATIONS

Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.  
 Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.  
 Gattefossé Sas, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.  
 Gattefossé Sas, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.  
 Gattefossé Sas, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.  
 Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," Clinical Pharmacy, 1990, vol. 9, No. 5, pp. 366-371.  
 Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," Journal of Pharmaceutical Sciences, vol. 86, No. 1, Jan. 1997, pp. 13-18.  
 Sasol Olefins & Surfactants GmbH, Excipients for Pharmaceuticals, 2010, 28 pages.  
 Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," Food and Chemical Toxicology, 72 (2014) pp. 40-50.  
 Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," Journal of Pharmaceutical Sciences, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.  
 ZRT Laboratory, Provider Data Sheet, About Dried Blood Spot Testing, 2014, 3 pages.

\* cited by examiner

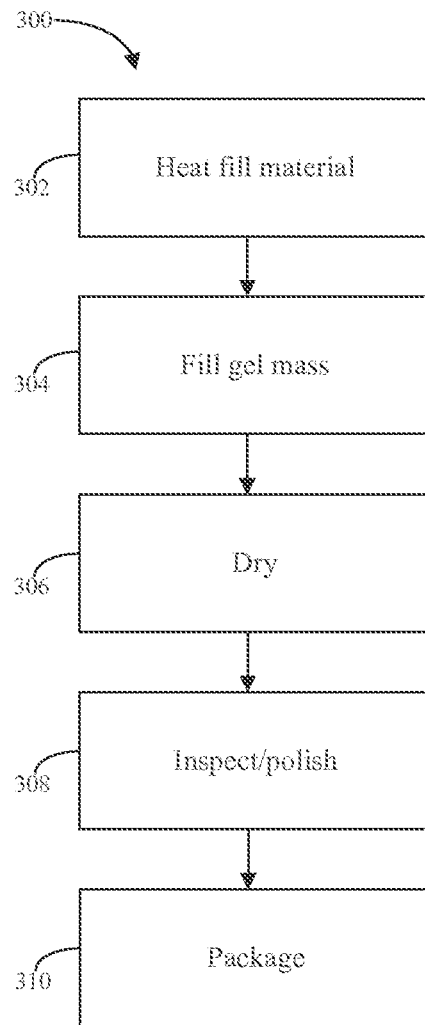


**Fig. 1**



**Fig. 2**





**Fig. 3**

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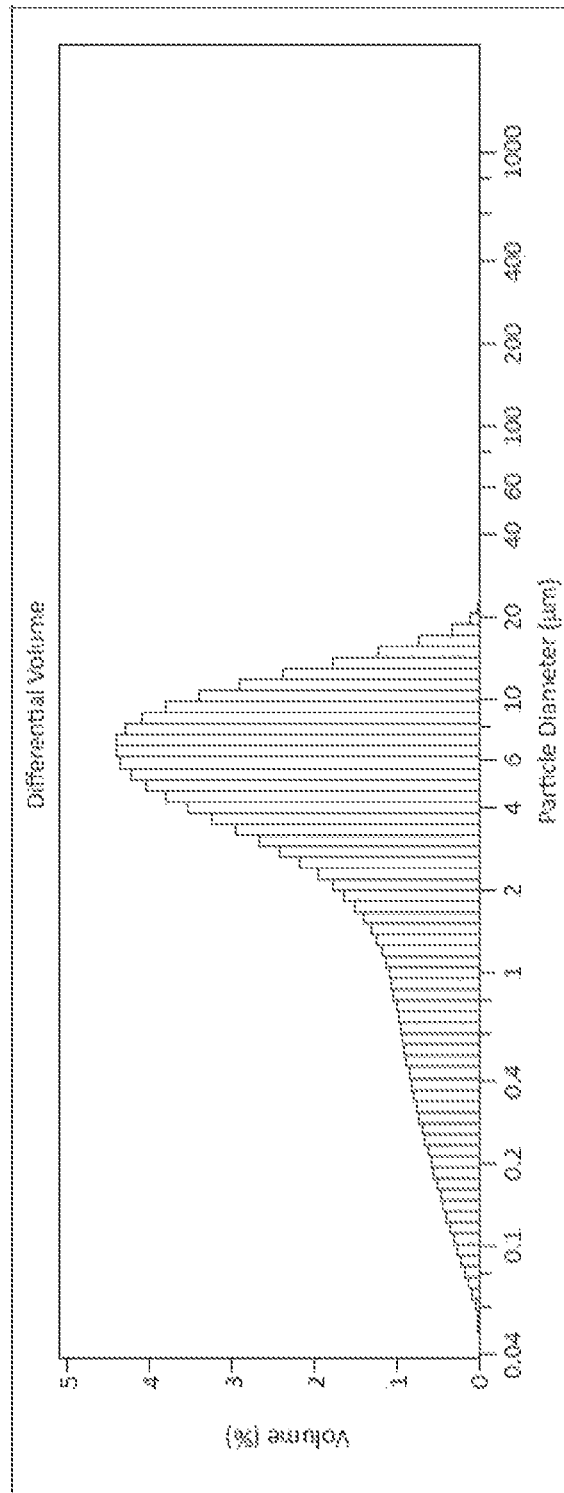


FIG. 4

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## NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

### CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/099,571, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Dec. 6, 2013, which is a continuation of U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

### FIELD OF THE INVENTION

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

### BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken

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daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

### SUMMARY OF THE INVENTION

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

### BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

### DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because

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many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

#### A. DEFINITIONS

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC,  $C_{max}$ , and optionally,  $T_{max}$ .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ $C_{max}$ ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ $T_{max}$ ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC,  $C_{max}$  and, optionally,  $T_{max}$  are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to estab-

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lished governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

#### B. DESCRIPTION AND PREFERRED EMBODIMENTS

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg:50 mg to about 2 mg:1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

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Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 $\beta$ -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for

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use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017  $\mu$ m to 2000  $\mu$ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4  $\mu$ m to 2000  $\mu$ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be



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combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol: Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Campul MCM; Capmul MCM and a non-ionic surfactant; and Campul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Campul MCM and Gelucire can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

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In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days



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identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

## EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

### Example 1

#### Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g

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solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

\*Literature reference—Salole, E.G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

### Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

### Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

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## 11

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:	6	Clear, after 14 days
Capmul PG8 (5:80:15)		
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol: Miglyol: Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:	12	Clear, after 12 days
Capmul PG8 (5:65:28)		
Transcutol:Miglyol 812:	12	Clear, after 12 days
Capmul PG8 (5:47:47)		
Capmul MCM	12	Clear after 12 days

## Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

## Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

## Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

## Example 7

## Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg

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progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM: Gelucire 44/14 (9:1)	86.4
Capmul MCM: Gelucire 44/14 (7:3)	70.5
Capmul MCM: Gelucire 44/14 (6:4)	57.4

## Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

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For example, Capmul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/- 2° C. Gelucire 44/14 may be added to the Capmul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Capmul MCM.

Heat may be removed from the Gelucire 44/14 and Capmul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Capmul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

## Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

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## Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

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## Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0  $\mu\text{m}$ , an X75 of 17.3  $\mu\text{m}$ , and an X25 of 5.3  $\mu\text{m}$ . The Beckman Device also yielded that the mean particle size is 11.8  $\mu\text{m}$ , the median particle size is 11.04  $\mu\text{m}$ , the mode particle size is 13.6  $\mu\text{m}$ , and the standard deviation is 7.8  $\mu\text{m}$ .

## Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

## Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:			100.000	200.00mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and

## Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279  $\mu\text{m}$ , an X75 of 7.442  $\mu\text{m}$ , and an X25 of 1.590  $\mu\text{m}$ . The Beckman Device also yielded that the mean particle size is 4.975  $\mu\text{m}$ , the median particle size is 4.279  $\mu\text{m}$ , the mode particle size is 6.453  $\mu\text{m}$ , and the standard deviation is 3.956  $\mu\text{m}$ . A graph of the particle distribution obtained is shown in FIG. 4.

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dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:		100.00	600.0 mg	6000.0	

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 16

Progesterone and Estradiol Combination Study  
Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the

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study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ±20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

## Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel



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vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.±3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.±10° C. The wedge temperature may be 38° C.±3° C. The drum cooling temperature may be 4° C.±2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thick-

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ness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A pharmaceutical composition comprising:

solubilized estradiol;  
suspended progesterone; and  
a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;  
wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises an effective amount of a monoglyceride, a diglyceride or a combination thereof containing an ester of a C6-C12 fatty acid.

2. The pharmaceutical composition of claim 1, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

3. The pharmaceutical composition of claim 1, wherein the formulation is formulated as a gelatin capsule.

4. The pharmaceutical composition of claim 1, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

5. The pharmaceutical composition of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

6. The pharmaceutical composition of claim 1, wherein the estradiol does not precipitate for at least 14 days.

7. A pharmaceutical composition comprising:

solubilized estradiol;  
suspended progesterone; and  
a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;  
wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises an effective amount of a monoglyceride thereof containing an ester of a C6-C12 fatty acid.

8. The pharmaceutical composition of claim 7, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

9. The pharmaceutical composition of claim 7, wherein the composition is formulated as a gelatin capsule.

10. The pharmaceutical composition of claim 7, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.



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11. The pharmaceutical composition of claim 7, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

12. The pharmaceutical composition of claim 7, wherein the estradiol does not precipitate for at least 14 days. 5

13. A pharmaceutical composition comprising:

solubilized estradiol;

suspended progesterone; and

a solubilizing agent;

wherein each of the estradiol and the suspended progesterone 10

are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;

wherein at least about 90% of the estradiol is solubilized in

the solubilizing agent; and

wherein the solubilizing agent comprising an effective 15

amount of a diglyceride containing an ester of a C6-C12

fatty acid.

14. The pharmaceutical composition of claim 13, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent. 20

15. The pharmaceutical composition of claim 13, wherein the composition is formulated in a gelatin capsule.

16. The pharmaceutical composition of claim 13, wherein the estradiol has a dosage strength of at least about 0.125 mg 25 and wherein the progesterone has a dosage strength of at least about 25 mg.

17. The pharmaceutical composition of claim 13, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1. 30

18. The pharmaceutical composition of claim 13, wherein the estradiol does not precipitate for at least 14 days.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,993,549 B2  
APPLICATION NO. : 14/475864  
DATED : March 31, 2015  
INVENTOR(S) : Brian A. Bernick et al.

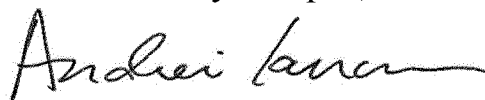
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this  
Second Day of April, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu  
*Director of the United States Patent and Trademark Office*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 8,993,549 B2  
APPLICATION NO. : 14/475864  
DATED : March 31, 2015  
INVENTOR(S) : Brian A. Bernick et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 20, Claim 7, Line 56: Delete “thereof”.

Signed and Sealed this  
Thirteenth Day of August, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu  
*Director of the United States Patent and Trademark Office*

# **EXHIBIT G**



US009006222B2

(12) **United States Patent**  
**Bernick et al.**

(10) **Patent No.:** **US 9,006,222 B2**  
(45) **Date of Patent:** **\*Apr. 14, 2015**

(54) **NATURAL COMBINATION HORMONE  
REPLACEMENT FORMULATIONS AND  
THERAPIES**

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(58) **Field of Classification Search**  
None

See application file for complete search history.

(56) **References Cited**

#### U.S. PATENT DOCUMENTS

1,967,351 A 7/1934 Doisy  
2,232,438 A 2/1941 Butenandt  
2,379,832 A 7/1945 Serini et al.  
2,649,399 A 8/1953 Grant et al.  
3,198,707 A 8/1965 Nomaine et al.  
3,478,070 A 11/1969 Smith et al.

3,526,648 A 9/1970 Bertin et al.  
3,710,795 A 1/1973 Higuchi et al.  
3,729,560 A 4/1973 Hagerman  
3,729,566 A 4/1973 Ericsson et al.  
3,755,573 A 8/1973 Berman  
3,755,575 A 8/1973 Lerner  
3,903,880 A 9/1975 Higuchi et al.  
3,916,898 A 11/1975 Robinson  
3,916,899 A 11/1975 Higuchi et al.  
3,921,636 A 11/1975 Zaffaroni  
3,923,997 A 12/1975 Meuly  
3,948,254 A 4/1976 Zaffaroni  
3,971,367 A 7/1976 Zaffaroni  
3,977,404 A 8/1976 Theeuwes  
3,993,072 A 11/1976 Zaffaroni  
4,008,719 A 2/1977 Theeuwes  
4,012,496 A 3/1977 Hartmann  
4,014,334 A 3/1977 Theeuwes et al.  
4,014,987 A 3/1977 Heller et al.  
4,016,251 A 4/1977 Higuchi et al.  
4,071,623 A 1/1978 Van Der Vies  
4,093,709 A 6/1978 Choi  
4,154,820 A 5/1979 Simoons  
4,155,991 A 5/1979 Schopflin et al.  
4,196,188 A 4/1980 Besins  
4,215,691 A 8/1980 Wong  
4,237,885 A 12/1980 Wong  
4,310,510 A 1/1982 Sherman et al.  
4,327,725 A 5/1982 Cortese et al.  
4,372,951 A 2/1983 Vorys  
4,384,096 A 5/1983 Sonnabend  
4,393,871 A 7/1983 Vorhauer

(Continued)

#### FOREIGN PATENT DOCUMENTS

BR PI 1001367-9 A2 7/2012  
CN 102258455 A 11/2011

(Continued)

#### OTHER PUBLICATIONS

PCCA, Apothogram, May 2014, pp. 1-14, Houston, TX.  
US 6,214,374, Apr. 10, 2001, Schmirler, et al. (withdrawn).  
Acog, McKinlay, et al., Practice Bulletin, Clinical Management  
Guidelines for Obstetrician-Gynecologists, Acog, No. 141, vol. 123,  
No. 1, Jan. 2014, Obstetrics & Gynecology.  
Araya-Sibaja, Andrea Manela, et al., Chemical Properties of  
Progesterone Selected Refer., SciFinder, 2014, American Chemical  
Society & US Natl. Lib. of Med.  
Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone  
Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn),  
Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.

(Continued)

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(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are pro-  
vided herein. Among others, the following formulations are  
provided herein: solubilized estradiol without progesterone;  
micronized progesterone without estradiol; micronized  
progesterone with partially solubilized progesterone; solubi-  
lized estradiol with micronized progesterone; solubilized  
estradiol with micronized progesterone in combination with  
partially solubilized progesterone; and solubilized estradiol  
with solubilized progesterone.

**12 Claims, 5 Drawing Sheets**

## US 9,006,222 B2

Page 2

(56)

## References Cited

## U.S. PATENT DOCUMENTS

4,402,695 A	9/1983	Wong	5,709,844 A	1/1998	Arbeit et al.
4,423,151 A	12/1983	Baranczuk	5,719,197 A	2/1998	Kanios et al.
4,449,980 A	5/1984	Millar et al.	5,735,801 A	4/1998	Caillouette
4,610,687 A	9/1986	Fogwell	5,739,176 A	4/1998	Dunn et al.
4,629,449 A	12/1986	Wong	5,744,463 A	4/1998	Bair
4,732,763 A	3/1988	Beck et al.	5,747,058 A	5/1998	Tipton et al.
4,738,957 A	4/1988	Laurent et al.	5,762,614 A	6/1998	Caillouette
4,756,907 A	7/1988	Beck et al.	5,770,176 A	6/1998	Nargessi
4,762,717 A	8/1988	Crowley	5,770,219 A	6/1998	Chiang et al.
4,788,062 A	11/1988	Gale et al.	5,770,220 A	6/1998	Meconi et al.
4,816,257 A	3/1989	Buster et al.	5,770,227 A	6/1998	Dong et al.
4,822,616 A	4/1989	Zimmermann et al.	5,776,495 A	7/1998	Duclos et al.
4,865,848 A	9/1989	Cheng et al.	5,780,044 A	7/1998	Yewey et al.
4,900,734 A	2/1990	Maxson et al.	5,780,050 A	7/1998	Jain et al.
4,906,475 A	3/1990	Kim	5,788,980 A	8/1998	Nabahi
4,942,158 A	7/1990	Sarpotdar et al.	5,788,984 A	8/1998	Guenther et al.
4,961,931 A	10/1990	Wong	5,789,442 A	8/1998	Garfield et al.
5,030,629 A	7/1991	Rajadhyaksha	5,811,416 A	9/1998	Chwalisz et al.
5,064,654 A	11/1991	Berner et al.	5,811,547 A	9/1998	Nakamichi et al.
5,108,995 A	4/1992	Casper	5,814,329 A	9/1998	Shah
5,128,138 A	7/1992	Blank	5,820,878 A	10/1998	Hirano et al.
5,130,137 A	7/1992	Crowley	5,827,200 A	10/1998	Caillouette
5,140,021 A	8/1992	Maxson et al.	5,840,327 A	11/1998	Gale et al.
5,211,952 A	5/1993	Pike et al.	5,843,468 A	12/1998	Burkoth et al.
5,252,334 A	10/1993	Chiang et al.	5,843,979 A	12/1998	Wille et al.
5,280,023 A	1/1994	Ehrlich et al.	5,858,394 A	1/1999	Lipp et al.
5,288,496 A	2/1994	Lewis	5,863,552 A	1/1999	Yue
5,340,584 A	8/1994	Spicer et al.	5,866,603 A	2/1999	Li et al.
5,340,585 A	8/1994	Pike et al.	5,882,676 A	3/1999	Lee et al.
5,340,586 A	8/1994	Pike et al.	5,885,612 A	3/1999	Meconi et al.
5,362,497 A	11/1994	Yamada et al.	5,888,533 A	3/1999	Dunn
5,382,573 A	1/1995	Casper	5,891,462 A	4/1999	Carrara
5,393,528 A	2/1995	Staab	5,891,868 A	4/1999	Cummings et al.
5,393,529 A	2/1995	Hoffmann et al.	5,898,038 A	4/1999	Yallampalli et al.
5,419,910 A	5/1995	Lewis	5,902,603 A	5/1999	Chen et al.
5,468,736 A	11/1995	Hodgen	5,904,931 A	5/1999	Lipp et al.
5,474,783 A	12/1995	Miranda et al.	5,906,830 A	5/1999	Farinas et al.
5,480,776 A	1/1996	Dullien	5,912,010 A	6/1999	Wille et al.
5,514,673 A	5/1996	Heckenmuller et al.	5,916,176 A	6/1999	Caillouette
5,516,528 A	5/1996	Hughes et al.	RE36,247 E	7/1999	Plunkett et al.
5,527,534 A	6/1996	Myhling	5,919,477 A	7/1999	Bevan et al.
5,529,782 A	6/1996	Staab	5,922,349 A	7/1999	Elliesen et al.
5,538,736 A	7/1996	Hoffmann et al.	5,928,666 A	7/1999	Farinas et al.
5,543,150 A	8/1996	Bologna et al.	5,942,243 A	8/1999	Shah
5,547,948 A	8/1996	Barcomb	5,952,000 A	9/1999	Venkateshwaran et al.
5,556,635 A	9/1996	Istin et al.	5,958,446 A	9/1999	Miranda et al.
5,565,199 A	10/1996	Page et al.	5,962,445 A	10/1999	Stewart
5,567,831 A	10/1996	Li	5,968,919 A	10/1999	Samour et al.
5,569,652 A	10/1996	Beier et al.	5,972,372 A	10/1999	Saleh et al.
5,580,572 A	12/1996	Mikler et al.	5,985,311 A	11/1999	Cordes et al.
5,582,592 A	12/1996	Kendrick	5,985,850 A	11/1999	Falk et al.
5,585,370 A	12/1996	Casper	5,985,861 A	11/1999	Levine et al.
5,595,759 A	1/1997	Wright et al.	5,989,568 A	11/1999	Breton et al.
5,595,970 A	1/1997	Garfield et al.	5,993,856 A	11/1999	Ragavan et al.
5,605,702 A	2/1997	Teillaud et al.	6,001,846 A	12/1999	Edwards et al.
5,607,691 A	3/1997	Hale et al.	6,007,835 A	12/1999	Bon Lapillonne et al.
5,607,693 A	3/1997	Bonte et al.	6,010,715 A	1/2000	Wick et al.
5,609,617 A	3/1997	Shealy et al.	6,013,276 A	1/2000	Math et al.
5,620,705 A	4/1997	Dong et al.	6,022,562 A	2/2000	Autant et al.
5,626,866 A	5/1997	Ebert et al.	6,024,974 A	2/2000	Li
5,629,021 A	5/1997	Wright	6,024,976 A	2/2000	Miranda et al.
5,633,011 A	5/1997	Dong et al.	6,028,057 A	2/2000	Burns
5,633,242 A	5/1997	Oettel et al.	6,030,948 A	2/2000	Mann
5,639,743 A	6/1997	Kaswan et al.	6,039,968 A	3/2000	Nabahi
5,653,983 A	8/1997	Meybeck et al.	6,040,340 A	3/2000	Chwalisz et al.
5,656,286 A	8/1997	Miranda et al.	6,056,972 A	5/2000	Hermesmyer
5,660,839 A	8/1997	Allec et al.	6,060,077 A	5/2000	Meignant
5,662,927 A	9/1997	Ehrlich et al.	6,068,853 A	5/2000	Giannos et al.
5,663,160 A	9/1997	Meybeck et al.	6,074,625 A	6/2000	Hawthorne et al.
5,676,968 A	10/1997	Lipp et al.	6,077,531 A	6/2000	Salin-Drouin
5,677,292 A	10/1997	Li et al.	6,080,118 A	6/2000	Blythe
5,686,097 A	11/1997	Taskovich et al.	6,083,178 A	7/2000	Caillouette
5,693,335 A	12/1997	Xia et al.	6,086,916 A	7/2000	Agnus et al.
5,694,947 A	12/1997	Lehtinen et al.	6,087,352 A	7/2000	Trout
5,700,480 A	12/1997	Hille et al.	6,090,404 A	7/2000	Meconi et al.
			6,096,338 A	8/2000	Lacy et al.
			6,106,848 A	8/2000	Preuilh et al.
			6,117,446 A	9/2000	Place
			6,117,450 A	9/2000	Dittgen et al.



## US 9,006,222 B2

Page 3

(56)

## References Cited

## U.S. PATENT DOCUMENTS

6,124,362	A	9/2000	Bradbury et al.	6,537,580	B1	3/2003	Savoir et al.
6,133,251	A	10/2000	Dittgen et al.	6,538,039	B2	3/2003	Laurent
6,133,320	A	10/2000	Yallampalli et al.	6,544,196	B2	4/2003	Caillouette
6,139,868	A	10/2000	Hoffmann	6,544,553	B1	4/2003	Hsia et al.
6,139,873	A	10/2000	Hughes, Jr. et al.	6,548,053	B1	4/2003	Stewart et al.
6,149,935	A	11/2000	Chiang et al.	6,548,491	B2	4/2003	Tanabe et al.
6,153,216	A	11/2000	Cordes et al.	6,551,611	B2	4/2003	Elliesen et al.
6,165,491	A	12/2000	Grasset et al.	6,555,131	B1	4/2003	Wolff et al.
6,165,975	A	12/2000	Adams et al.	6,562,367	B1	5/2003	Wolff et al.
6,187,323	B1	2/2001	Aiache et al.	6,562,370	B2	5/2003	Luo et al.
6,187,339	B1	2/2001	de Haan et al.	6,562,790	B2	5/2003	Chein
6,190,331	B1	2/2001	Caillouette	6,569,463	B2	5/2003	Patel et al.
6,201,072	B1	3/2001	Rathi et al.	6,583,129	B1	6/2003	Mazer et al.
6,217,886	B1	4/2001	Onyuksel et al.	6,586,006	B2	7/2003	Roser et al.
6,225,297	B1	5/2001	Stockemann et al.	6,589,549	B2	7/2003	Shih et al.
6,227,202	B1	5/2001	Matapurkar	6,593,317	B1	7/2003	De Ziegler et al.
6,228,383	B1	5/2001	Hansen et al.	6,599,519	B1	7/2003	Seo et al.
6,228,852	B1	5/2001	Shaak	6,610,670	B2	8/2003	Backensfeld et al.
6,242,509	B1	6/2001	Berger et al.	6,610,674	B1	8/2003	Schreiber
6,245,811	B1	6/2001	Horrobin et al.	6,610,652	B2	10/2003	Savoir et al.
6,262,115	B1	7/2001	Guittard et al.	6,635,274	B1	10/2003	Masiz et al.
6,267,984	B1	7/2001	Beste et al.	6,638,528	B1	10/2003	Kanios
6,274,165	B1	8/2001	Meconi et al.	6,638,536	B2	10/2003	Savoir et al.
6,277,418	B1	8/2001	Markaverich et al.	6,645,528	B1	11/2003	Straub et al.
6,283,927	B1	9/2001	Caillouette	6,649,155	B1	11/2003	Dunlop et al.
6,287,588	B1	9/2001	Shih et al.	6,653,298	B2	11/2003	Potter et al.
6,287,693	B1	9/2001	Savoir et al.	6,656,929	B1	12/2003	Agnus et al.
6,294,188	B1	9/2001	Ragavan et al.	6,660,726	B2	12/2003	Hill et al.
6,294,192	B1	9/2001	Patel et al.	6,663,608	B2	12/2003	Rathbone et al.
6,294,550	B1	9/2001	Place et al.	6,663,895	B2	12/2003	Savoir et al.
6,299,900	B1	10/2001	Reed et al.	6,682,757	B1	1/2004	Wright
6,303,132	B1	10/2001	Nelson	6,692,763	B1	2/2004	Cummings et al.
6,303,588	B1	10/2001	Danielov	6,708,822	B1	3/2004	Muni
6,306,841	B1	10/2001	Place et al.	6,720,001	B2	4/2004	Chen et al.
6,306,914	B1	10/2001	Ziegler et al.	6,740,333	B2	5/2004	Beckett et al.
6,309,669	B1	10/2001	Setterstrom et al.	6,737,081	B2	6/2004	Griffin et al.
6,309,848	B1	10/2001	Howett et al.	6,743,448	B2	6/2004	Kryger
6,312,703	B1	11/2001	Orthoefer	6,743,815	B2	6/2004	Huebner et al.
6,328,987	B1	12/2001	Marini	6,747,018	B2	6/2004	Tanabe et al.
6,342,491	B1	1/2002	Dey et al.	6,750,291	B2	6/2004	Kim et al.
6,344,211	B1	2/2002	Hille	6,756,208	B2	6/2004	Griffin et al.
6,372,209	B1	4/2002	Chrisope	6,776,164	B2	8/2004	Bunt et al.
6,372,245	B1	4/2002	Bowman et al.	6,787,152	B2	9/2004	Kirby et al.
6,372,246	B1	4/2002	Wei	6,805,877	B2	10/2004	Massara et al.
6,387,390	B1	5/2002	Deaver et al.	6,809,085	B1	10/2004	Elson et al.
6,402,705	B1	6/2002	Caillouette	6,818,226	B2	10/2004	Elson et al.
6,416,778	B1	7/2002	Ragavan et al.	6,821,524	B2	11/2004	Marini
6,420,352	B1	7/2002	Knowles	6,841,716	B1	1/2005	Tsutsumi
6,423,039	B1	7/2002	Rathbone et al.	6,844,334	B2	1/2005	Hill et al.
6,423,683	B1	7/2002	Heaton et al.	6,855,703	B1	2/2005	Hill et al.
6,432,438	B1	8/2002	Shukla	6,860,859	B2	3/2005	Mehrotra et al.
6,436,633	B1	8/2002	Kreider et al.	6,866,865	B2	3/2005	Hsia et al.
6,440,454	B1	8/2002	Santoro et al.	6,869,969	B2	3/2005	Huebner et al.
6,444,224	B1	9/2002	Rathbone et al.	6,878,518	B2	4/2005	Whitehead
6,444,234	B1	9/2002	Kirby et al.	6,901,278	B1	5/2005	Notelovitz
6,451,300	B1	9/2002	Dunlop et al.	6,905,705	B2	6/2005	Palm et al.
6,451,339	B2	9/2002	Patel et al.	6,911,211	B2	6/2005	Eini et al.
6,451,779	B1	9/2002	Hesch	6,911,438	B2	6/2005	Wright
6,455,246	B1	9/2002	Howett et al.	6,923,988	B2	8/2005	Patel et al.
6,455,517	B1	9/2002	Tanabe et al.	6,924,274	B2	8/2005	Lardy et al.
6,465,004	B1	10/2002	Rossi Montero et al.	6,932,983	B1	8/2005	Straub et al.
6,465,005	B1	10/2002	Biali et al.	6,939,558	B2	9/2005	Massara et al.
6,465,006	B1	10/2002	Zhang et al.	6,943,021	B2	9/2005	Klausner et al.
6,468,526	B2	10/2002	Chrisope	6,958,327	B1	10/2005	Hillisch et al.
6,469,016	B1	10/2002	Place et al.	6,960,337	B2	11/2005	Daniels et al.
6,472,434	B1	10/2002	Place et al.	6,962,691	B1	11/2005	Lulla et al.
6,479,232	B1	11/2002	Howett et al.	6,962,908	B2	11/2005	Aloba et al.
6,495,160	B2	12/2002	Esposito et al.	6,967,194	B1	11/2005	Matsuo et al.
6,500,814	B1	12/2002	Hesch	6,974,569	B2	12/2005	Dunlop et al.
6,503,896	B1	1/2003	Tanabe et al.	6,977,250	B2	12/2005	Rodriguez
6,511,969	B1	1/2003	Hermesmyer	6,978,945	B2	12/2005	Wong et al.
6,521,250	B2	2/2003	Meconi et al.	6,995,149	B1	2/2006	Endrikat et al.
6,526,980	B1	3/2003	Tracy et al.	7,004,321	B1	2/2006	Palm et al.
6,528,094	B1	3/2003	Savoir et al.	7,005,429	B2	2/2006	Dey et al.
6,531,149	B1	3/2003	Kirstgen et al.	7,011,846	B2	3/2006	Shojaei et al.
				7,018,992	B2	3/2006	Koch et al.
				7,030,104	B2	4/2006	Gray et al.
				7,030,157	B2	4/2006	Ke et al.
				RE39,104	E	5/2006	Duclos et al.

## US 9,006,222 B2

Page 4

(56)

## References Cited

## U.S. PATENT DOCUMENTS

7,074,779 B2	7/2006	Sui et al.	7,939,104 B2	5/2011	Barbera et al.
7,083,590 B1	8/2006	Bunt et al.	7,943,602 B2	5/2011	Bunschoten et al.
7,091,213 B2	8/2006	Metcalf, III et al.	7,943,604 B2	5/2011	Coelingh Bennink et al.
7,094,228 B2	8/2006	Zhang et al.	7,960,368 B2	6/2011	Nickisch et al.
7,097,853 B1	8/2006	Garbe et al.	7,989,436 B2	8/2011	Hill et al.
7,101,342 B1	9/2006	Caillouette	7,989,487 B2	8/2011	Welsh et al.
7,105,573 B2	9/2006	Krajcik et al.	8,022,053 B2	9/2011	Mueller et al.
7,135,190 B2	11/2006	Piao et al.	8,048,017 B2	11/2011	Xu
7,153,522 B1	12/2006	Ikeura et al.	8,048,869 B2	11/2011	Bunschoten et al.
7,163,681 B2	1/2007	Giles-Komar	8,063,030 B2	11/2011	Ellman
7,163,699 B2	1/2007	Besse	8,071,576 B2	12/2011	Coelingh Bennink et al.
7,175,850 B2	2/2007	Cevc	8,071,729 B2	12/2011	Giles-Komar et al.
7,179,799 B2	2/2007	Hill et al.	8,075,916 B2	12/2011	Song et al.
7,196,074 B2	3/2007	Blye et al.	8,075,917 B2	12/2011	Chung et al.
7,198,800 B1	4/2007	Ko	8,076,317 B2	12/2011	Kulmann
7,198,801 B2	4/2007	Carrara et al.	8,076,319 B2	12/2011	Leonard
7,226,910 B2	6/2007	Wilson et al.	8,080,553 B2	12/2011	Keith et al.
7,247,625 B2	7/2007	Zhang et al.	8,088,605 B2	1/2012	Beaudet et al.
7,250,446 B2	7/2007	Sangita et al.	8,096,940 B2	1/2012	Josephson et al.
7,267,829 B2	9/2007	Kirby et al.	8,101,209 B2	1/2012	Legrand et al.
7,300,926 B2	11/2007	Prokai et al.	8,101,773 B2	1/2012	Smith
7,303,763 B2	12/2007	Ho	8,114,152 B2	2/2012	Furst
7,317,037 B2	1/2008	Fensome et al.	8,114,434 B2	2/2012	Sasaki et al.
7,329,654 B2	2/2008	Kanojia et al.	8,114,442 B2	2/2012	Tucker et al.
7,335,650 B2	2/2008	Potter et al.	8,119,741 B2	2/2012	Pavlin
7,374,779 B2	5/2008	Chen et al.	8,124,118 B2	2/2012	Lennernaes et al.
7,378,404 B2	5/2008	Peters	8,124,595 B2	2/2012	Boissonneau
7,381,427 B2	6/2008	Ancira et al.	8,147,561 B2	4/2012	Binmoeller
7,387,789 B2	6/2008	Klose et al.	8,148,546 B2	4/2012	Schuster et al.
7,388,006 B2	6/2008	Schmees et al.	8,158,613 B2	4/2012	Staniforth et al.
7,414,043 B2	8/2008	Kosemund et al.	8,158,614 B2	4/2012	Lambert et al.
7,427,413 B2	9/2008	Savoir et al.	8,163,722 B2	4/2012	Savoir et al.
7,427,609 B2	9/2008	Leonard	8,177,449 B2	5/2012	Bayly et al.
7,429,576 B2	9/2008	Labrie	8,182,833 B2	5/2012	Hermesmeyer
7,431,941 B2	10/2008	Besins et al.	8,187,615 B2	5/2012	Friedman
7,456,159 B2	11/2008	Houze et al.	8,195,403 B2	6/2012	Ishikawa et al.
7,459,445 B2	12/2008	Hill et al.	8,202,736 B2	6/2012	Mousa et al.
7,465,587 B2	12/2008	Imrich	8,217,024 B2	7/2012	Ahmed et al.
7,470,433 B2	12/2008	Carrara et al.	8,221,785 B2	7/2012	Chien
7,485,666 B2	2/2009	Villanueva et al.	8,222,008 B2	7/2012	Thoene
7,497,855 B2	3/2009	Ausiello et al.	8,222,237 B2	7/2012	Nickisch et al.
7,498,303 B2	3/2009	Arnold et al.	8,227,454 B2	7/2012	Hill et al.
7,534,765 B2	5/2009	Gregg et al.	8,227,509 B2	7/2012	Castro et al.
7,534,780 B2	5/2009	Wyrwa et al.	8,241,664 B2	8/2012	Dudley et al.
7,550,142 B2	6/2009	Giles-Komar et al.	8,247,393 B2	8/2012	Ahmed et al.
7,563,565 B1	7/2009	Matsuo et al.	8,257,724 B2	9/2012	Cromack et al.
7,569,274 B2	8/2009	Besse et al.	8,257,725 B2	9/2012	Cromack et al.
7,572,779 B2	8/2009	Aloba et al.	8,268,352 B2	9/2012	Vaya et al.
7,572,780 B2	8/2009	Hermesmeyer	8,268,806 B2	9/2012	Labrie
7,589,082 B2	9/2009	Savoir et al.	8,268,878 B2	9/2012	Armer et al.
7,671,027 B2	3/2010	Loumaye	8,273,730 B2	9/2012	Fernandez et al.
7,674,783 B2	3/2010	Hermesmeyer	8,287,888 B2	10/2012	Song et al.
7,687,281 B2	3/2010	Roth et al.	8,288,366 B2	10/2012	Chochinov et al.
7,687,485 B2	3/2010	Levinson et al.	8,318,898 B2	11/2012	Fasel et al.
7,694,683 B2	4/2010	Callister et al.	8,324,193 B2	12/2012	Lee Sepsick et al.
7,704,983 B1	4/2010	Hodgen et al.	8,329,680 B2	12/2012	Evans et al.
7,727,720 B2	6/2010	Dhallan	8,337,814 B2	12/2012	Osbakken et al.
7,732,408 B2	6/2010	Josephson et al.	8,344,007 B2	1/2013	Tang et al.
7,749,989 B2	7/2010	Hill et al.	8,349,820 B2	1/2013	Zeun et al.
7,767,656 B2	8/2010	Shoichet et al.	8,353,863 B2	1/2013	Imran
7,799,769 B2	9/2010	White et al.	8,357,723 B2	1/2013	Satyam
7,815,936 B2	10/2010	Hasenzahl et al.	8,361,995 B2	1/2013	Schramm
7,815,949 B2	10/2010	Cohen	8,362,091 B2	1/2013	Tamarkin et al.
7,829,115 B2	11/2010	Besins et al.	8,372,424 B2	2/2013	Berry et al.
7,829,116 B2	11/2010	Griswold et al.	8,372,806 B2	2/2013	Boehler et al.
RE42,012 E	12/2010	Deaver et al.	8,377,482 B2	2/2013	Laurie et al.
7,850,992 B2	12/2010	Kim et al.	8,377,994 B2	2/2013	Gray et al.
7,854,753 B2	12/2010	Kraft et al.	8,394,759 B2	3/2013	Barathur et al.
7,858,607 B2	12/2010	Mamchur	8,415,332 B2	4/2013	Diliberti et al.
RE42,072 E	1/2011	Deaver et al.	8,420,111 B2	4/2013	Hermesmeyer
7,862,552 B2	1/2011	McIntyre et al.	8,435,561 B2	5/2013	Besins et al.
7,867,990 B2	1/2011	Schultz et al.	8,435,972 B2	5/2013	Stein et al.
7,871,643 B2	1/2011	Lizio et al.	8,449,879 B2	5/2013	Laurent Applegate et al.
7,879,830 B2	2/2011	Wiley	8,450,108 B2	5/2013	Boyce
7,884,093 B2	2/2011	Creasy et al.	8,454,945 B2	6/2013	McCook et al.
			8,455,468 B2	6/2013	Hoffman et al.
			8,461,138 B2	6/2013	Boissonneau
			8,476,252 B2	7/2013	Achleitner et al.
			8,481,488 B2	7/2013	Carter

## US 9,006,222 B2

Page 5

(56)

## References Cited

## U.S. PATENT DOCUMENTS

8,486,374 B2	7/2013	Tamarkin et al.	2003/0003139 A1	1/2003	Lipp et al.
8,486,442 B2	7/2013	Matsushita et al.	2003/0004145 A1	1/2003	Leonard
8,492,368 B2	7/2013	Vanlandingham et al.	2003/0007994 A1	1/2003	Bunt et al.
8,507,467 B2	8/2013	Matsui et al.	2003/0027772 A1	2/2003	Breton
8,512,693 B2	8/2013	Capito et al.	2003/0044453 A1	3/2003	Dittgen et al.
8,512,754 B2	8/2013	Needham	2003/0049307 A1	3/2003	Gyurik
8,518,376 B2	8/2013	Tamarkin et al.	2003/0064097 A1	4/2003	Patel et al.
8,536,159 B2	9/2013	Li et al.	2003/0072760 A1	4/2003	Sirbasku
8,540,967 B2	9/2013	Barrett et al.	2003/0073248 A1	4/2003	Roth et al.
8,541,400 B2	9/2013	Johansson et al.	2003/0073673 A1	4/2003	Hesch
8,551,462 B2	10/2013	Goldstein et al.	2003/0077297 A1	4/2003	Chen et al.
8,557,281 B2	10/2013	Halliday et al.	2003/0078245 A1	4/2003	Bennink et al.
8,568,374 B2	10/2013	De Graaff et al.	2003/0091620 A1	5/2003	Fikstad et al.
8,591,951 B2	11/2013	Kohn et al.	2003/0091640 A1	5/2003	Ramanathan et al.
8,613,951 B2	12/2013	Zale et al.	2003/0092691 A1	5/2003	Besse et al.
8,633,178 B2	1/2014	Bernick et al.	2003/0096012 A1	5/2003	Besse et al.
8,633,180 B2	1/2014	Li et al.	2003/0104048 A1	6/2003	Patel et al.
8,636,787 B2	1/2014	Sabaria	2003/0109507 A1	6/2003	Franke et al.
8,636,982 B2	1/2014	Tamarkin et al.	2003/0113268 A1	6/2003	Buenaflae et al.
8,653,129 B2	2/2014	Fein et al.	2003/0114420 A1	6/2003	Salvati et al.
8,658,627 B2	2/2014	Voskuhl	2003/0114430 A1	6/2003	MacLeod et al.
8,658,628 B2	2/2014	Baucom	2003/0124182 A1	7/2003	Shojaei et al.
8,663,681 B2	3/2014	Ahmed et al.	2003/0124191 A1	7/2003	Besse et al.
8,663,692 B1	3/2014	Mueller et al.	2003/0130558 A1	7/2003	Massara et al.
8,663,703 B2	3/2014	Lerner et al.	2003/0144258 A1	7/2003	Heil et al.
8,664,207 B2	3/2014	Li et al.	2003/0157157 A1	8/2003	Luo et al.
8,669,293 B2	3/2014	Levy et al.	2003/0166509 A1	9/2003	Edwards et al.
8,679,552 B2	3/2014	Guthery	2003/0170295 A1	9/2003	Kim et al.
8,697,127 B2	4/2014	Sah	2003/0175329 A1	9/2003	Azarnoff et al.
8,697,710 B2	4/2014	Li et al.	2003/0175333 A1	9/2003	Shefer et al.
8,703,105 B2	4/2014	Tamarkin et al.	2003/0180352 A1	9/2003	Patel et al.
8,709,385 B2	4/2014	Tamarkin et al.	2003/0181353 A1	9/2003	Nyce
8,709,451 B2	4/2014	Nam et al.	2003/0181728 A1	9/2003	Salvati et al.
8,715,735 B2	5/2014	Funk et al.	2003/0191096 A1	10/2003	Leonard et al.
8,721,331 B2	5/2014	Raghuprasad	2003/0195177 A1	10/2003	Leonard et al.
8,722,021 B2	5/2014	Friedman et al.	2003/0215496 A1	11/2003	Patel et al.
8,734,846 B2	5/2014	Ali et al.	2003/0219402 A1	11/2003	Rutter
8,735,381 B2	5/2014	Podolski	2003/0220297 A1	11/2003	Berstein et al.
8,741,336 B2	6/2014	Dipierro et al.	2003/0224057 A1	12/2003	Martin-Letellier et al.
8,741,373 B2	6/2014	Bromley et al.	2003/0224059 A1	12/2003	Lerner et al.
8,753,661 B2	6/2014	Steinmueller et al.	2003/0225047 A1	12/2003	Caubel et al.
8,784,882 B2	7/2014	Mattern	2003/0225048 A1	12/2003	Caubel et al.
2001/0005728 A1	6/2001	Guittard et al.	2003/0225050 A1	12/2003	Grawe et al.
2001/0009673 A1	7/2001	Lipp et al.	2003/0228686 A1	12/2003	Klausner et al.
2001/0021816 A1	9/2001	Caillouette	2003/0229057 A1	12/2003	Caubel et al.
2001/0023261 A1	9/2001	Ryoo et al.	2003/0235596 A1	12/2003	Gao et al.
2001/0027189 A1	10/2001	Bennink et al.	2003/0236236 A1	12/2003	Chen et al.
2001/0029357 A1	10/2001	Bunt et al.	2004/0009960 A1	1/2004	Heil et al.
2001/0031747 A1	10/2001	DeZiegler et al.	2004/0022820 A1	2/2004	Anderson
2001/0034340 A1	10/2001	Pickar	2004/0034001 A1	2/2004	Karara
2001/0053383 A1	12/2001	Miranda et al.	2004/0037881 A1	2/2004	Guittard et al.
2001/0056068 A1	12/2001	Chwalisz et al.	2004/0039356 A1	2/2004	Maki et al.
2002/0012710 A1	1/2002	Lansky	2004/0043043 A1	3/2004	Schlyter et al.
2002/0026158 A1	2/2002	Rathbone et al.	2004/0043943 A1	3/2004	Guittard et al.
2002/0028788 A1	3/2002	Bunt et al.	2004/0044080 A1	3/2004	Place et al.
2002/0035070 A1	3/2002	Gardlik et al.	2004/0048900 A1	3/2004	Flood
2002/0058648 A1	5/2002	Hammerly	2004/0052824 A1	3/2004	Chacra-Vernet et al.
2002/0058926 A1	5/2002	Rathbone et al.	2004/0073024 A1	4/2004	Metcalfe, III et al.
2002/0076441 A1	6/2002	Shih et al.	2004/0077605 A1	4/2004	Salvati et al.
2002/0102308 A1	8/2002	Wei et al.	2004/0077606 A1	4/2004	Salvati et al.
2002/0107230 A1	8/2002	Waldon et al.	2004/0087548 A1	5/2004	Salvati et al.
2002/0114803 A1	8/2002	Deaver et al.	2004/0087564 A1	5/2004	Wright et al.
2002/0119174 A1	8/2002	Gardlik et al.	2004/0089308 A1	5/2004	Welch
2002/0119198 A1	8/2002	Gao et al.	2004/0092494 A9	5/2004	Dudley
2002/0132801 A1	9/2002	Heil et al.	2004/0092583 A1	5/2004	Shanahan-Prendergast
2002/0137749 A1	9/2002	Levinson et al.	2004/0097468 A1	5/2004	Wimalawansa
2002/0142017 A1	10/2002	Simonnet	2004/0101557 A1	5/2004	Gibson et al.
2002/0151530 A1	10/2002	Leonard et al.	2004/0106542 A1	6/2004	Deaver et al.
2002/0156394 A1	10/2002	Mehrotra et al.	2004/0110732 A1	6/2004	Masini-Eteve et al.
2002/0169150 A1	11/2002	Pickar	2004/0131670 A1	7/2004	Gao
2002/0169205 A1	11/2002	Chwalisz et al.	2004/0138103 A1	7/2004	Patt
2002/0173510 A1	11/2002	Levinson et al.	2004/0142012 A1	7/2004	Bunt et al.
2002/0193356 A1	12/2002	Van Beek et al.	2004/0146539 A1	7/2004	Gupta
2002/0193758 A1	12/2002	Sandberg	2004/0146894 A1	7/2004	Warrington et al.
2002/0197286 A1	12/2002	Brandman et al.	2004/0161435 A1	8/2004	Gupta
			2004/0176324 A1	9/2004	Salvati et al.
			2004/0176336 A1	9/2004	Rodriguez
			2004/0185104 A1	9/2004	Piao et al.
			2004/0191207 A1	9/2004	Lipari et al.

## US 9,006,222 B2

Page 6

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2004/0191276	A1	9/2004	Muni	2006/0089337	A1	4/2006	Casper et al.
2004/0198706	A1	10/2004	Carrara	2006/0093678	A1	5/2006	Chickering, III et al.
2004/0210280	A1	10/2004	Liedtke	2006/0100180	A1	5/2006	Nubbemeyer et al.
2004/0213744	A1	10/2004	Lulla et al.	2006/0106004	A1	5/2006	Brody et al.
2004/0219124	A1	11/2004	Gupta	2006/0110415	A1	5/2006	Gupta
2004/0225140	A1	11/2004	Fernandez et al.	2006/0111424	A1	5/2006	Salvati et al.
2004/0234606	A1	11/2004	Levine et al.	2006/0121102	A1	6/2006	Chiang
2004/0241219	A1	12/2004	Hille et al.	2006/0121626	A1	6/2006	Imrich
2004/0253319	A1	12/2004	Netke et al.	2006/0134188	A1	6/2006	Podhaisky et al.
2004/0259817	A1	12/2004	Waldon et al.	2006/0135619	A1	6/2006	Kick et al.
2004/0266745	A1	12/2004	Schwanitz et al.	2006/0165744	A1	7/2006	Jamil et al.
2005/0003003	A1	1/2005	Basu et al.	2006/0193789	A1	8/2006	Tamarkin et al.
2005/0004088	A1	1/2005	Hesch	2006/0194775	A1	8/2006	Tofovic et al.
2005/0009800	A1	1/2005	Thumbek et al.	2006/0204557	A1	9/2006	Gupta et al.
2005/0014729	A1	1/2005	Pulaski	2006/0233743	A1	10/2006	Kelly
2005/0020550	A1	1/2005	Morris et al.	2006/0233841	A1	10/2006	Brodbeck et al.
2005/0020552	A1	1/2005	Aschkenasay et al.	2006/0235037	A1	10/2006	Purandare et al.
2005/0021009	A1	1/2005	Massara et al.	2006/0240111	A1	10/2006	Fernandez et al.
2005/0025833	A1	2/2005	Aschkenasay et al.	2006/0246122	A1	11/2006	Langguth et al.
2005/0031651	A1	2/2005	Gervais et al.	2006/0247216	A1	11/2006	Haj-Yehia
2005/0042173	A1	2/2005	Besse et al.	2006/0247221	A1	11/2006	Coelingh Bennink et al.
2005/0042268	A1	2/2005	Aschkenasay et al.	2006/0251581	A1	11/2006	McIntyre et al.
2005/0048116	A1	3/2005	Straub et al.	2006/0252049	A1	11/2006	Shuler et al.
2005/0054991	A1	3/2005	Tobyn et al.	2006/0257472	A1	11/2006	Nielsen
2005/0079138	A1	4/2005	Chickering, III et al.	2006/0275218	A1	12/2006	Tamarkin et al.
2005/0085453	A1	4/2005	Govindarajan	2006/0275360	A1	12/2006	Ahmed et al.
2005/0101579	A1	5/2005	Shippen	2006/0276414	A1	12/2006	Coelingh Bennink et al.
2005/0113350	A1	5/2005	Duesterberg et al.	2006/0280771	A1	12/2006	Groenewegen et al.
2005/0118244	A1	6/2005	Theobald et al.	2006/0280797	A1	12/2006	Shoichet et al.
2005/0118272	A1	6/2005	Besse et al.	2006/0280800	A1	12/2006	Nagi et al.
2005/0129756	A1	6/2005	Podhaisky et al.	2006/0292223	A1	12/2006	Woolfson et al.
2005/0152956	A1	7/2005	Dudley	2007/0004693	A1	1/2007	Woolfson et al.
2005/0153946	A1	7/2005	Hirsh et al.	2007/0004694	A1	1/2007	Woolfson et al.
2005/0164977	A1	7/2005	Coelingh Bennink	2007/0009559	A1	1/2007	Li et al.
2005/0182105	A1	8/2005	Nirschl et al.	2007/0009594	A1	1/2007	Grubb et al.
2005/0186141	A1	8/2005	Gonda et al.	2007/0010550	A1	1/2007	McKenzie
2005/0187267	A1	8/2005	Hamann et al.	2007/0014839	A1	1/2007	Bracht
2005/0192253	A1	9/2005	Salvati et al.	2007/0015698	A1	1/2007	Kleinman et al.
2005/0192310	A1	9/2005	Gavai et al.	2007/0021360	A1	1/2007	Nyce et al.
2005/0196434	A1	9/2005	Brierre	2007/0027201	A1	2/2007	McComas et al.
2005/0207990	A1	9/2005	Funke et al.	2007/0031491	A1	2/2007	Levine et al.
2005/0214384	A1	9/2005	Juturu et al.	2007/0037780	A1	2/2007	Ebert et al.
2005/0220825	A1	10/2005	Funke et al.	2007/0037782	A1	2/2007	Hibino et al.
2005/0220900	A1	10/2005	Popp et al.	2007/0042038	A1	2/2007	Besse
2005/0222106	A1	10/2005	Bracht	2007/0060589	A1	3/2007	Purandare et al.
2005/0239747	A1	10/2005	Yang et al.	2007/0066628	A1	3/2007	Zhang et al.
2005/0239758	A1	10/2005	Roby	2007/0066637	A1	3/2007	Zhang et al.
2005/0244360	A1	11/2005	Billoni	2007/0066675	A1	3/2007	Zhang et al.
2005/0244522	A1	11/2005	Carrara et al.	2007/0078091	A1	4/2007	Hubler et al.
2005/0245902	A1	11/2005	Cornish et al.	2007/0088029	A1	4/2007	Balog et al.
2005/0250746	A1	11/2005	Iammatteo	2007/0093548	A1	4/2007	Diffendal et al.
2005/0250750	A1	11/2005	Cummings et al.	2007/0116729	A1	5/2007	Palepu
2005/0250753	A1	11/2005	Fink et al.	2007/0116829	A1	5/2007	Prakash et al.
2005/0256028	A1	11/2005	Yun et al.	2007/0128263	A1	6/2007	Gargiulo et al.
2005/0266078	A1	12/2005	Jorda et al.	2007/0154533	A1	7/2007	Dudley
2005/0266088	A1	12/2005	Hinrichs et al.	2007/0167418	A1	7/2007	Ferguson
2005/0271597	A1	12/2005	Keith	2007/0178166	A1	8/2007	Bernstein et al.
2005/0271598	A1	12/2005	Frieman et al.	2007/0184558	A1	8/2007	Roth et al.
2005/0272685	A1	12/2005	Hung	2007/0185068	A1	8/2007	Ferguson et al.
2005/0272712	A1	12/2005	Grubb et al.	2007/0190022	A1	8/2007	Bacopoulos et al.
2006/0009428	A1	1/2006	Grubb et al.	2007/0191319	A1	8/2007	Ke et al.
2006/0014728	A1	1/2006	Chwalisz et al.	2007/0196415	A1	8/2007	Chen et al.
2006/0018937	A1	1/2006	Friedman et al.	2007/0196433	A1	8/2007	Ron et al.
2006/0019978	A1	1/2006	Balog	2007/0207225	A1	9/2007	Squadrito
2006/0020002	A1	1/2006	Salvati et al.	2007/0225281	A1	9/2007	Zhang et al.
2006/0030615	A1	2/2006	Fensome et al.	2007/0232574	A1	10/2007	Galey et al.
2006/0034889	A1	2/2006	Jo et al.	2007/0238713	A1	10/2007	Gast et al.
2006/0034904	A1	2/2006	Weimann	2007/0243229	A1	10/2007	Smith et al.
2006/0051391	A1	3/2006	Dvoskin et al.	2007/0248658	A1	10/2007	Zurdo Schroeder et al.
2006/0052341	A1	3/2006	Cornish et al.	2007/0254858	A1	11/2007	Cronk
2006/0069031	A1	3/2006	Loumaye	2007/0255197	A1	11/2007	Humberstone et al.
2006/0078618	A1	4/2006	Constantinides et al.	2007/0264309	A1	11/2007	Chollet et al.
2006/0083778	A1	4/2006	Allison et al.	2007/0264345	A1	11/2007	Eros et al.
2006/0084704	A1	4/2006	Shih et al.	2007/0264349	A1	11/2007	Lee et al.
2006/0088580	A1	4/2006	Meconi et al.	2007/0286819	A1	12/2007	DeVries et al.
				2007/0287688	A1	12/2007	Chan et al.
				2007/0287789	A1	12/2007	Jones et al.
				2007/0292359	A1	12/2007	Friedman et al.
				2007/0292387	A1	12/2007	Jon et al.



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(56)

## References Cited

## U.S. PATENT DOCUMENTS

2007/0292461	A1	12/2007	Tamarkin et al.	2009/0214474	A1	8/2009	Jennings
2007/0292493	A1	12/2007	Brierre	2009/0227025	A1	9/2009	Nichols et al.
2007/0298089	A1	12/2007	Saeki et al.	2009/0227550	A1	9/2009	Mattern
2008/0026035	A1	1/2008	Chollet et al.	2009/0232897	A1	9/2009	Sahoo et al.
2008/0026040	A1	1/2008	Farr et al.	2009/0258096	A1	10/2009	Cohen
2008/0026062	A1	1/2008	Farr et al.	2009/0264395	A1	10/2009	Creasy et al.
2008/0038219	A1	2/2008	Mosbaugh et al.	2009/0269403	A1	10/2009	Shaked et al.
2008/0038350	A1	2/2008	Gerecke et al.	2009/0285772	A1	11/2009	Phiasivongsa et al.
2008/0039405	A1	2/2008	Langley et al.	2009/0285869	A1	11/2009	Trimble
2008/0050317	A1	2/2008	Tamarkin et al.	2009/0318558	A1	12/2009	Kim et al.
2008/0051351	A1	2/2008	Ghisalberti	2009/0324714	A1	12/2009	Liu et al.
2008/0063607	A1	3/2008	Tamarkin et al.	2009/0325916	A1	12/2009	Zhang et al.
2008/0069779	A1	3/2008	Tamarkin et al.	2010/0008985	A1	1/2010	Pellikaan et al.
2008/0069791	A1	3/2008	Beissert	2010/0028360	A1	2/2010	Atwood
2008/0085877	A1	4/2008	Bortz	2010/0034838	A1	2/2010	Staniforth et al.
2008/0095831	A1	4/2008	McGraw	2010/0034880	A1	2/2010	Sintov et al.
2008/0095838	A1	4/2008	Abou Chacra-Vernet	2010/0040671	A1	2/2010	Ahmed et al.
2008/0113953	A1	5/2008	DeVries et al.	2010/0048523	A1	2/2010	Bachman et al.
2008/0114050	A1	5/2008	Fensome et al.	2010/0055138	A1	3/2010	Margulies et al.
2008/0119537	A1	5/2008	Zhang et al.	2010/0074959	A1	3/2010	Hansom et al.
2008/0125402	A1	5/2008	Diliberti et al.	2010/0086501	A1	4/2010	Chang et al.
2008/0138379	A1	6/2008	Jennings-Spring	2010/0086599	A1	4/2010	Huempel et al.
2008/0138390	A1	6/2008	Hsu et al.	2010/0092568	A1	4/2010	Lerner et al.
2008/0139392	A1	6/2008	Acosta Zara et al.	2010/0119585	A1	5/2010	Hille et al.
2008/0145423	A1	6/2008	Khan et al.	2010/0129320	A1	5/2010	Phiasivongsa et al.
2008/0153789	A1	6/2008	Dmowski et al.	2010/0105071	A1	6/2010	Chen et al.
2008/0175814	A1	7/2008	Phiasivongsa et al.	2010/0136105	A1	6/2010	Chen et al.
2008/0175905	A1	7/2008	Liu et al.	2010/0137265	A1	6/2010	Leonard
2008/0175908	A1	7/2008	Liu et al.	2010/0137271	A1	6/2010	Chen et al.
2008/0188829	A1	8/2008	Creasy	2010/0143420	A1	6/2010	Shenoy et al.
2008/0206156	A1	8/2008	Cronk	2010/0143481	A1	6/2010	Shenoy et al.
2008/0206159	A1	8/2008	Tamarkin et al.	2010/0150993	A1	6/2010	Theobald et al.
2008/0206161	A1	8/2008	Tamarkin et al.	2010/0152144	A1	6/2010	Hermesmyer
2008/0214512	A1	9/2008	Seitz et al.	2010/0168228	A1	7/2010	Bose et al.
2008/0220069	A1	9/2008	Allison	2010/0183723	A1	7/2010	Laurent-Applegate
2008/0226698	A1	9/2008	Tang et al.	2010/0184736	A1	7/2010	Coelingh Bennink et al.
2008/0227763	A1	9/2008	Lanquetin et al.	2010/0190758	A1	7/2010	Fausser et al.
2008/0234199	A1	9/2008	Katamreddym et al.	2010/0204326	A1	8/2010	D Souza
2008/0234240	A1	9/2008	Duesterberg et al.	2010/0210994	A1	8/2010	Zarif
2008/0255078	A1	10/2008	Katamreddym et al.	2010/0221195	A1	9/2010	Tamarkin et al.
2008/0255089	A1	10/2008	Katamreddym et al.	2010/0227797	A1	9/2010	Axelsson et al.
2008/0261931	A1	10/2008	Hedner et al.	2010/0240626	A1	9/2010	Kulkarni et al.
2008/0299220	A1	12/2008	Tamarkin et al.	2010/0247482	A1	9/2010	Cui et al.
2008/0306036	A1	12/2008	Katamreddym et al.	2010/0247632	A1	9/2010	Dong et al.
2008/0312197	A1	12/2008	Rodriguez	2010/0247635	A1	9/2010	Rosenberg et al.
2008/0312198	A1	12/2008	Rodriguez	2010/0255085	A1	10/2010	Liu et al.
2008/0319078	A1	12/2008	Katamreddym et al.	2010/0273730	A1	10/2010	Hsu et al.
2009/0004246	A1	1/2009	Woolfson et al.	2010/0278759	A1	11/2010	Murad
2009/0010968	A1	1/2009	Allart et al.	2010/0279988	A1	11/2010	Setiawan et al.
2009/0011041	A1	1/2009	Musaeva et al.	2010/0291191	A1	11/2010	Shoichet et al.
2009/0017120	A1	1/2009	Trimble et al.	2010/0292199	A1	11/2010	Leverd et al.
2009/0022683	A1	1/2009	Song et al.	2010/0303825	A9	12/2010	Sirbasku et al.
2009/0047357	A1	2/2009	Tomohira et al.	2010/0312137	A1	12/2010	Gilmour et al.
2009/0053294	A1	2/2009	Prendergast	2010/0316724	A1	12/2010	Whitfield et al.
2009/0060982	A1	3/2009	Ron et al.	2010/0322884	A1	12/2010	Dipietro et al.
2009/0060997	A1	3/2009	Seitz et al.	2010/0330168	A1	12/2010	Gicquel et al.
2009/0068118	A1	3/2009	Eini et al.	2011/0028439	A1	2/2011	Witt-Enderby et al.
2009/0081206	A1	3/2009	Leibovitz	2011/0039814	A1	2/2011	Huatan et al.
2009/0081278	A1	3/2009	De Graaff et al.	2011/0053845	A1	3/2011	Levine et al.
2009/0081303	A1	3/2009	Savoir et al.	2011/0076775	A1	3/2011	Stewart et al.
2009/0092656	A1	4/2009	Klamerus et al.	2011/0076776	A1	3/2011	Stewart et al.
2009/0093440	A1	4/2009	Murad	2011/0086825	A1	4/2011	Chatroux
2009/0098069	A1	4/2009	Vacca	2011/0087192	A1	4/2011	Uhland et al.
2009/0099106	A1	4/2009	Phiasivongsa et al.	2011/0091555	A1	4/2011	De Luigi Bruschi et al.
2009/0099149	A1	4/2009	Liu et al.	2011/0098258	A1	4/2011	Masini Eteve et al.
2009/0130029	A1	5/2009	Tamarkin et al.	2011/0098631	A1	4/2011	McIntyre et al.
2009/0131385	A1	5/2009	Voskuhl	2011/0104268	A1	5/2011	Pachot et al.
2009/0137478	A1	5/2009	Bernstein et al.	2011/0104289	A1	5/2011	Savoir Vilboeuf et al.
2009/0137538	A1	5/2009	Klamerus et al.	2011/0130372	A1	6/2011	Agostinacchio et al.
2009/0143344	A1	6/2009	Chang	2011/0135719	A1	6/2011	Besins et al.
2009/0175799	A1	7/2009	Tamarkin et al.	2011/0142945	A1	6/2011	Chen et al.
2009/0181088	A1	7/2009	Song et al.	2011/0152840	A1	6/2011	Lee et al.
2009/0186081	A1	7/2009	Holm et al.	2011/0158920	A1	6/2011	Morley et al.
2009/0197843	A1	8/2009	Notelovitz et al.	2011/0171140	A1	7/2011	Illum et al.
2009/0203658	A1	8/2009	Marx et al.	2011/0182997	A1	7/2011	Lewis et al.
				2011/0190201	A1	8/2011	Hyde et al.
				2011/0195031	A1	8/2011	Du
				2011/0195114	A1	8/2011	Carrara et al.
				2011/0195944	A1	8/2011	Mura et al.

## US 9,006,222 B2

Page 8

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2011/0217341	A1	9/2011	Sah	2013/0004619	A1	1/2013	Chow et al.
2011/0238003	A1	9/2011	Bruno Raimondi et al.	2013/0011342	A1	1/2013	Tamarkin et al.
2011/0244043	A1	10/2011	Xu et al.	2013/0017239	A1	1/2013	Viladot Petit et al.
2011/0250256	A1	10/2011	Hyun Oh et al.	2013/0022674	A1	1/2013	Dudley et al.
2011/0250259	A1	10/2011	Buckman	2013/0023505	A1	1/2013	Garfield et al.
2011/0250274	A1	10/2011	Shaked et al.	2013/0023823	A1	1/2013	Simpson et al.
2011/0256092	A1	10/2011	Phiasivongsa et al.	2013/0028850	A1	1/2013	Tamarkin et al.
2011/0262373	A1	10/2011	Umbert Millet	2013/0029947	A1	1/2013	Nachhaegari et al.
2011/0262494	A1	10/2011	Achleitner et al.	2013/0029957	A1	1/2013	Giliyar et al.
2011/0268665	A1	11/2011	Tamarkin et al.	2013/0045266	A1	2/2013	Choi et al.
2011/0275584	A1	11/2011	Wilckens et al.	2013/0045953	A1	2/2013	Sitruk Ware et al.
2011/0281832	A1	11/2011	Li et al.	2013/0059795	A1	3/2013	Lo et al.
2011/0287094	A1	11/2011	Penhasi et al.	2013/0064897	A1	3/2013	Binay
2011/0293720	A1	12/2011	General et al.	2013/0072466	A1	3/2013	Choi et al.
2011/0294738	A1	12/2011	Ren et al.	2013/0084257	A1	4/2013	Ishida et al.
2011/0300167	A1	12/2011	McMurry et al.	2013/0085123	A1	4/2013	Li et al.
2011/0301087	A1	12/2011	McBride et al.	2013/0089574	A1	4/2013	Schmidt Gollwitzer et al.
2011/0306579	A1	12/2011	Stein	2013/0090318	A1	4/2013	Ulmann et al.
2011/0311592	A1	12/2011	Birbara	2013/0102781	A1	4/2013	Bevill et al.
2011/0312927	A1	12/2011	Nachhaegari et al.	2013/0108551	A1	5/2013	Langereis et al.
2011/0312928	A1	12/2011	Nachhaegari et al.	2013/0116215	A1	5/2013	Coma et al.
2011/0318405	A1	12/2011	Erwin	2013/0116222	A1	5/2013	Arnold et al.
2011/0318431	A1	12/2011	Gulati	2013/0122051	A1	5/2013	Abidi et al.
2012/0009276	A1	1/2012	De Groote	2013/0123175	A1	5/2013	Hill et al.
2012/0015350	A1	1/2012	Nabatiyan et al.	2013/0123220	A1	5/2013	Queiroz
2012/0021041	A1	1/2012	Rossi et al.	2013/0123351	A1	5/2013	Dewitt
2012/0028888	A1	2/2012	Janz et al.	2013/0129818	A1	5/2013	Bernick et al.
2012/0028910	A1	2/2012	Combal et al.	2013/0131027	A1	5/2013	Pakkalin et al.
2012/0028936	A1	2/2012	Gloger et al.	2013/0131028	A1	5/2013	Snyder et al.
2012/0045532	A1	2/2012	Cohen	2013/0131029	A1	5/2013	Bakker et al.
2012/0046264	A1	2/2012	Simes et al.	2013/0149314	A1	6/2013	Bullerdiek et al.
2012/0046518	A1	2/2012	Yoakum et al.	2013/0164225	A1	6/2013	Tamarkin et al.
2012/0269878	A2	2/2012	Cantor et al.	2013/0164346	A1	6/2013	Lee et al.
2012/0052077	A1	3/2012	Truitt et al.	2013/0165744	A1	6/2013	Carson et al.
2012/0058171	A1	3/2012	De Graaff et al.	2013/0178452	A1	7/2013	King
2012/0058962	A1	3/2012	Cumming et al.	2013/0183254	A1	7/2013	Zhou et al.
2012/0058979	A1	3/2012	Keith et al.	2013/0183325	A1	7/2013	Bottoni et al.
2012/0064135	A1	3/2012	Levin et al.	2013/0189193	A1	7/2013	Tamarkin et al.
2012/0065179	A1	3/2012	Andersson	2013/0189196	A1	7/2013	Tamarkin et al.
2012/0087872	A1	4/2012	Tamarkin et al.	2013/0189230	A1	7/2013	Shoichet et al.
2012/0101073	A1	4/2012	Mannion et al.	2013/0189368	A1	7/2013	Mosqueira et al.
2012/0121517	A1	5/2012	Song et al.	2013/0210709	A1	8/2013	McMurry et al.
2012/0121692	A1	5/2012	Xu et al.	2013/0216550	A1	8/2013	Penninger et al.
2012/0122829	A1	5/2012	Taravella et al.	2013/0216596	A1	8/2013	Viladot Petit et al.
2012/0128625	A1	5/2012	Shalwitz et al.	2013/0224177	A1	8/2013	Kim et al.
2012/0128654	A1	5/2012	Terpstra et al.	2013/0224257	A1	8/2013	Sah et al.
2012/0128683	A1	5/2012	Shantha	2013/0224268	A1	8/2013	Alam et al.
2012/0128733	A1	5/2012	Perrin et al.	2013/0224300	A1	8/2013	Maggio
2012/0128777	A1	5/2012	Keck et al.	2013/0225412	A1	8/2013	Sardari Lodriche et al.
2012/0129773	A1	5/2012	Geier et al.	2013/0225542	A1	8/2013	Poegh et al.
2012/0129819	A1	5/2012	Vancaillie et al.	2013/0226113	A1	8/2013	Schumacher et al.
2012/0136013	A1	5/2012	Li et al.	2013/0243696	A1	9/2013	Wang et al.
2012/0142645	A1	6/2012	Marx	2013/0245253	A1	9/2013	Marx et al.
2012/0148670	A1	6/2012	Kim et al.	2013/0245570	A1	9/2013	Jackson
2012/0149748	A1	6/2012	Shanler et al.	2013/0261096	A1	10/2013	Merian et al.
2012/0172343	A1	7/2012	Lindenthal et al.	2013/0266645	A1	10/2013	Becker et al.
2012/0184515	A1	7/2012	Klar et al.	2013/0267485	A1	10/2013	Da Silva Maia Filho
2012/0231052	A1	9/2012	Sitruk Ware et al.	2013/0273167	A1	10/2013	Lee et al.
2012/0232011	A1	9/2012	Kneissel et al.	2013/0274211	A1	10/2013	Burman et al.
2012/0232042	A1	9/2012	Klar et al.	2013/0280213	A1	10/2013	Voskuhl
2012/0263679	A1	10/2012	Marlow et al.	2013/0316374	A1	11/2013	Penninger et al.
2012/0269721	A1	10/2012	Weng et al.	2013/0317065	A1	11/2013	Tatani et al.
2012/0277249	A1	11/2012	Andersson et al.	2013/0317315	A1	11/2013	Lu et al.
2012/0277727	A1	11/2012	Doshi et al.	2013/0324565	A1	12/2013	Li et al.
2012/0283671	A1	11/2012	Shibata et al.	2013/0331363	A1	12/2013	Li et al.
2012/0295911	A1	11/2012	Mannion et al.	2013/0338124	A1	12/2013	Li et al.
2012/0301517	A1	11/2012	Zhang et al.	2013/0345187	A1	12/2013	Rodriguez Oquendo
2012/0301538	A1	11/2012	Gordon Beresford et al.	2014/0018335	A1	1/2014	Tatani et al.
2012/0302535	A1	11/2012	Caufriez et al.	2014/0024590	A1	1/2014	Weidhaas et al.
2012/0316130	A1	12/2012	Hendrix	2014/0031289	A1	1/2014	Song et al.
2012/0316496	A1	12/2012	Hoffmann et al.	2014/0031323	A1	1/2014	Perez
2012/0321579	A1	12/2012	Edelson et al.	2014/0066416	A1	3/2014	Leunis et al.
2012/0322779	A9	12/2012	Voskuhl	2014/0072531	A1	3/2014	Kim et al.
2012/0328549	A1	12/2012	Edelson et al.	2014/0079686	A1	3/2014	Barman et al.
2012/0329738	A1	12/2012	Liu	2014/0088058	A1	3/2014	Maurizio
				2014/0088059	A1	3/2014	Perumal et al.
				2014/0094426	A1	4/2014	Drummond et al.
				2014/0100159	A1	4/2014	Conrad
				2014/0100206	A1	4/2014	Bernick et al.



## US 9,006,222 B2

Page 9

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2014/0113889 A1 4/2014 Connor et al.  
 2014/0127185 A1 5/2014 Stein et al.  
 2014/0127280 A1 5/2014 Duesterberg et al.  
 2014/0127308 A1 5/2014 Opara et al.  
 2014/0128798 A1 5/2014 Janson et al.  
 2014/0148491 A1 5/2014 Valia et al.  
 2014/0186332 A1 7/2014 Ezrin et al.  
 2014/0187487 A1 7/2014 Shoichet et al.  
 2014/0193523 A1 7/2014 Henry  
 2014/0194396 A1 7/2014 Li et al.  
 2014/0206616 A1 7/2014 Ko et al.

## FOREIGN PATENT DOCUMENTS

EP 0275716 A1 7/1988  
 EP 0622075 A1 11/1994  
 EP 0785211 A1 1/1996  
 EP 0811381 A1 6/1997  
 EP 0785212 A1 7/1997  
 EP 1094781 B1 7/2008  
 EP 2191833 A1 6/2010  
 GB 1589946 A1 2/1921  
 GB 452238 A 8/1936  
 GB 720561 A 12/1954  
 GB 848881 A 9/1960  
 GB 874368 A 8/1961  
 IN 216026 A 3/2008  
 IN 2005KO00053 A 9/2009  
 IN 244217 A 11/2010  
 WO 9011064 A1 10/1990  
 WO 9317686 A1 9/1993  
 WO 9422426 A1 10/1994  
 WO 9530409 A1 11/1995  
 WO 9609826 A2 4/1996  
 WO WO9619975 7/1996  
 WO 9630000 A1 10/1996  
 WO 9705491 2/1997  
 WO 9743989 A1 11/1997  
 WO 9810293 A1 3/1998  
 WO 9832465 A1 7/1998  
 WO 9851280 A1 11/1998  
 WO 9932072 A1 7/1999  
 WO 9939700 A1 8/1999  
 WO 9942109 A1 8/1999  
 WO 9943304 9/1999  
 WO 9948477 A1 9/1999  
 WO 9953910 A2 10/1999  
 WO 0038659 A1 11/1999  
 WO 9963974 A2 12/1999  
 WO 0001351 A1 1/2000  
 WO 0006175 A1 2/2000  
 WO 0045795 A2 8/2000  
 WO 0050007 A1 8/2000  
 WO 0059577 A1 10/2000  
 WO 0137808 A1 11/2000  
 WO 0076522 A1 12/2000  
 WO 0154699 A1 8/2001  
 WO 0160325 A1 8/2001  
 WO 0207700 A2 2/2002  
 WO 0211768 A1 2/2002  
 WO 0222132 A2 3/2002  
 WO 0240008 A2 5/2002  
 WO WO0241878 5/2002  
 WO 02053131 A1 7/2002  
 WO 02078602 A2 10/2002  
 WO 2002078604 A2 10/2002  
 WO WO03028667 4/2003  
 WO 03041718 A1 5/2003  
 WO 03041741 A1 5/2003  
 WO 03068186 A1 8/2003  
 WO 03077923 A1 9/2003  
 WO 03082254 A1 10/2003  
 WO 03092588 A2 11/2003  
 WO WO2004014432 2/2004

WO 2004017983 A1 3/2004  
 WO 2005027911 A1 3/2004  
 WO 2004032897 A2 4/2004  
 WO 2004052336 A2 6/2004  
 WO 2004054540 A2 7/2004  
 WO 2004080413 A2 9/2004  
 WO 2005030175 A1 4/2005  
 WO 2005087194 A1 9/2005  
 WO 2005087199 A2 9/2005  
 WO WO2005081825 9/2005  
 WO 2005105059 A1 11/2005  
 WO 2005115335 A1 12/2005  
 WO 2005120470 A1 12/2005  
 WO 2005120517 A1 12/2005  
 WO 2006013369 A2 2/2006  
 WO 2006034090 A1 3/2006  
 WO 2006036899 A2 4/2006  
 WO 2006053172 A2 5/2006  
 WO 2006105615 A1 10/2006  
 WO 2006113505 A2 10/2006  
 WO 2006138686 A1 12/2006  
 WO 2006138735 A2 12/2006  
 WO 2007045027 A1 4/2007  
 WO 2007103294 A2 9/2007  
 WO WO2007120868 10/2007  
 WO 2007123790 A1 11/2007  
 WO 2007124250 A2 11/2007  
 WO 2007144151 A1 12/2007  
 WO 2008049516 A3 5/2008  
 WO 2008152444 A2 12/2008  
 WO 2009002542 A1 12/2008  
 WO 2009036311 A1 3/2009  
 WO 2009040818 4/2009  
 WO 2009069006 A2 6/2009  
 WO 2009098072 A2 8/2009  
 WO 2009133352 A2 11/2009  
 WO 2010033188 A2 3/2010  
 WO WO2010146872 12/2010  
 WO 2011000210 A1 1/2011  
 WO 2011073995 A2 6/2011  
 WO 2011120084 A1 10/2011  
 WO 2011128336 A1 10/2011  
 WO 2012009778 A2 1/2012  
 WO 2012024361 A1 2/2012  
 WO WO2012055814 A1 5/2012  
 WO WO2012055840 A1 5/2012  
 WO WO2012065740 5/2012  
 WO WO2012098090 A1 7/2012  
 WO WO2012116277 A1 8/2012  
 WO WO2012118563 A2 9/2012  
 WO WO2012120365 A1 9/2012  
 WO WO2012127501 A2 9/2012  
 WO WO2012156561 A1 11/2012  
 WO WO2012156822 A1 11/2012  
 WO WO2012158483 A2 11/2012  
 WO WO2012166909 A1 12/2012  
 WO WO2012170578 A1 12/2012  
 WO WO2013011501 A1 1/2013  
 WO WO2013025449 A1 2/2013  
 WO WO2013028639 A1 2/2013  
 WO WO2013035101 A1 3/2013  
 WO WO2013044067 A1 3/2013  
 WO WO2013045404 A2 4/2013  
 WO WO2013059285 A1 4/2013  
 WO WO2013063279 A1 5/2013  
 WO WO2013064620 A1 5/2013  
 WO WO2013071281 A1 5/2013  
 WO WO2013088254 6/2013  
 WO WO2013102665 A1 7/2013  
 WO WO2013106437 A1 7/2013  
 WO WO2013113690 8/2013  
 WO WO2013124415 A1 8/2013  
 WO WO2013127727 A1 9/2013  
 WO WO2013127728 A1 9/2013  
 WO WO2013144356 A1 10/2013  
 WO WO2013149258 A2 10/2013  
 WO WO2013158454 A2 10/2013  
 WO WO2013170052 A1 11/2013  
 WO 2013192248 A1 12/2013

## US 9,006,222 B2

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(56)

## References Cited

## FOREIGN PATENT DOCUMENTS

WO	2013192249	A1	12/2013
WO	2013192250	A1	12/2013
WO	2013192251	A1	12/2013
WO	WO2013178587	A1	12/2013
WO	WO2013181449	A1	12/2013
WO	WO2014001904	A1	1/2014
WO	WO2014004424	A1	1/2014
WO	WO2014009434	A1	1/2014
WO	WO2014018569	A1	1/2014
WO	WO2014018570	A1	1/2014
WO	WO2014018571	A2	1/2014
WO	WO2014018856	A1	1/2014
WO	WO2014018932	A2	1/2014
WO	WO2014031958	A1	2/2014
WO	WO2014041120	A1	3/2014
WO	WO2014052792	A1	4/2014
WO	WO2014056897	A1	4/2014
WO	WO2014066442	A2	5/2014
WO	WO2014074846	A1	5/2014
WO	WO2014076231	A1	5/2014
WO	WO2014076569	A2	5/2014
WO	WO2014081598	A1	5/2014
WO	WO2014086739	A1	6/2014
WO	WO2014093114	A1	6/2014
WO	WO2014104784	A1	7/2014

## OTHER PUBLICATIONS

Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.

Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.

Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.

Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, Steroids, vol. 46(6), pp. 967-974, Dec. 1985.

Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , Vibrational Spectroscopy 8, Elsevier, pp. 263, 1995.

Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, Bollettino Chimico Farmaceutico, vol. 122(1) pp. 20-26, 1983 SciFinder.

Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.

Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? J. Steroid Biochem. Mol. Biol. (2013), Elsevier.

BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.

Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, Acta Pharm. Jugosl., vol. 40 pp. 71-94, 1990.

Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.

Buray, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, Am J Obstet Gynecol, vol. 180(6) part 1, pp. 1504-1511, 1999.

Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, Revista Mexicana de Fisica, 50, Suplemento 1 pp. 1-3, 2004.

Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.

Commodari, Fernando, Comparison of 17B-estradiol structures from x-ray diffraction and solution NMR, Magn. Reson. Chem., vol. 43, pp. 444-450, 2005, Wiley InterScience.

Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, The Lancet, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.

Dideberg, O, et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , J. Appl. Cryst. vol. 4 pp. 80, 1971.

Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , Inter. Journal of Pharmaceutics, Elsevier, vol. 363, pp. 40-49, 2009.

Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, J. Am. Chem. Soc., vol. 103 pp. 6705-6712, Jun. 1981.

Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , J. Thermal Anal., vol. 37 pp. 1869-1875, 1991, Wiley.

Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, SciFinder, Pharmaceutica Acta Helvetica, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.

Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.

Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, Pharmaceutical Research, vol. 20(2), 2003, Plenum Pub. Corp.

FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.

Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.

Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, Journal of General Internal Medicine, vol. 22, pp. 1030-1034, 2007.

Giron, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, Thermochimica Acta, vol. 248 pp. 1-59, 1995, Elsevier.

Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, J. Pharmaceutical & Biomedical Anal., vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.

Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.

Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, Acta Cryst., vol. 17 pp. 1610, 1964.

Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.

Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, Pharm Res, vol. 31 pp. 795-808, 2014, Springer Science.

Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.

Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, Jour. of Mag. Resonance, vol. 63, pp. 333-342, 1985, Academic Press, Inc.

Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.

Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, Mol. Pharmacology, vol. 8 pp. 438-445, Academic Press, Inc., 1972.

Hulsman, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, Pharmaceutical Development and Tech., vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.

Idder, Salima, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.

Johnson, William S, et al., Racemic Progesterone, Tetrahedron Letters No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.

Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, Drug Dev. & Indus. Pharm., vol. 10(5) pp. 771-787, 1984, Marcel Dekker.

## US 9,006,222 B2

Page 11

(56)

## References Cited

## OTHER PUBLICATIONS

- Korkmaz, Filiz, Biophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyan, P.N., Stability indicating HPTLC method for the estimation of estradiol, Journal of Pharmaceutical and Biomedical Analysis, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminiewski, R, et al., EPR Study of the Stable Radical in a  $\gamma$ -Irradiated Single Crystal of Progesterone, Jour. of Mag. Resonance, vol. 46 pp. 300-305, 1982, Academic Press.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone, SciFinder Scholar Search, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Struhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M, et al., The light sensitivity of corticosteroids in crystalline form, Pharmaceutica Acta Helvetica, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S, et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , Intl. J. of Pharmaceut., vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, AAPS PharmSciTech, vol. 11, No. 3, Sep. 2010.
- USP Monographs: Progesterone, USP29, [www.pharmacopeia.cn/v29240/usp29nf24s0\\_m69870.html](http://www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html), search done: Feb. 25, 2014.
- Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . Fertility and Sterility, vol. 75(6) pp. 1065, Jun. 2001.
- Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, Thermochimica Acta 485, Elsevier, pp. 57, 2009.
- Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, J. of Pharmaceutical Sciences, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, Handbook of Aqueous Solubility Data, Solutions, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
- Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, Journal of Steroid Biochem & Mol Biology, vol. 86 pp. 477-486, 2003.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Saffey Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of *Thevetia peruviana* and *Hura crepitans* Seed oils using GC-FID, Fountain Journal of Nat. and Appl. Sciences, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopocia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index>[Feb. 3, 2014 1:37:50 PM].
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro—Edible-Oil-Refining—ISO—TUV—Austria.
- Corn Refiners Assoc, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Eqbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Ferrari, Roseli AP, et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, Sci. Agric., vol. 62(3), pp. 291-295, 2005, Piracicaba, Braz.
- Gunstone, Frank D, et al., Vegetable Oils In Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, Clean Techn Environ Policy, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, Obstetrics & Gynecology, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, Springerlink.com, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, Journal of Food Science, vol. 47, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Lauroyl Polyoxylglycerides, Saffey Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate—Corn Oil, Lot G0L404, Jul. 2013.
- Weber, E.J., Corn Lipids, Cereal Chem., vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, Drug Development and Industrial Pharmacy, Early Online, pp. 1-8, 2014, Informa Healthcare.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- International Search Report and Written Opinion for related International Application No. PCT/US12/066406 dated Jan. 24, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/023309 dated Apr. 9, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/046442 dated Nov. 1, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/046443 dated Oct. 31, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/046444 dated Oct. 31, 2013.
- International Search Report and Written Opinion for related International Application No. PCT/US13/046445 dated Nov. 1, 2013.
- USPTO; Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.
- USPTO; Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002.

## US 9,006,222 B2

Page 12

(56)

## References Cited

## OTHER PUBLICATIONS

USPTO; Notice of Allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002.

Acarturk, "Mucoadhesive Vaginal Drug Delivery Systems," Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Exiler-Ankara, Recent Patents on Drug Delivery & Formulation 2009, 3, 193-205.

Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," Drug Development and Industrial Pharmacy, 35(5):525-547 (May 2009). Abstract Only.

Azure Pharma, Inc., "ELESTRIN™—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archivaid=11885>, 26 pages (Aug. 2009).

Bhavnani, et al., "Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ERα and ERβ", Endocrinology, 149(10): 4857-4870 (Oct. 2008).

Bhavnani, et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," J Clin Endocrinol Metab, Mar. 2012, 97(3).

Tahition Noni, "Body Balance Cream," [http://products.tni.com/dominican\\_republic/sa\\_spanish/nonistore/product/3438/3416/](http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/), (undated), 1 page.

Nugen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, (undated), 3 pages.

Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," J. Kor. Pharm. Sci., 35(3):173-177, (2005).

Committee of Obstetric Practice, Committee Opinion—No. 522, Obstetrics & Gynecology, 119(4):879-882 (Apr. 2012).

Diramio, "Polyethylene Glycol Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia—Masters of Science Thesis, 131 pages (2004). [http://athenaum.libs.uga.edu/bitstream/handle/10724/7820/diramio\\_jackie\\_a\\_200412\\_ms.pdf?sequence=1](http://athenaum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1).

Du, et al., "Percutaneous Progesterone Delivery Via Cream or Gel Application in Postmenopausal Women: A Randomized Cross-Over Study of Progesterone Levels in Serum, Whole Blood, Saliva, and Capillary Blood," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 11, (Feb. 2013).

Fotherby, K., "Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy," Contraception 1996;54:59-69.

Fuchs, et al., "The Effects of on Estrogen and Glycolic Acid Cream on the Fociol Skin of Postmenopausal Women: A Randonized Histologic Study," Pharmacology / Cosmetology, vol. 5, No. 1, 2006.

Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," International Journal of Pharmaceutics, 147(2):165-171 (Feb. 1997). Abstract Only.

Hargrove, et al., Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone, vol. 73, No. 4, pp. 606-612 Apr. 1989.

Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," Critical Reviews in Toxicology, 30(3):307-345 (2000).

Kincl, et al., "Increasing Oral Bioavailability of Progesterone by Formulation," Pergamon Press, Journal of Steroid Biochemistry, 1978, vol. 9, pp. 83-84.

Knuth et al., "Hydrogel Delivery Systems for Vaginal and Oral Applications: Formulation and Biological Considerations," Advanced Drug Delivery Reviews, 11(1-2):137-167 (Jul.-Aug. 1993). Abstract Only.

Lucy et al., "Gonadotropin-Releasing Hormone at Estrus: Luteinizing Hormone, Estradiol, and Progesterone During the Peri-estrus and Postinsemination Periods in Dairy Cattle," Biol Reprod. 35(2):300-311 (1986). Abstract Only.

Position Statement, "Management of Symptomatic Vulvovaginal Atrophy: 2013 Position Statement of the North American Menopause

Society," Menopause: The Journal of the North American Menopause Society, vol. 20, No. 9, pp. 888-902, Jun. 2013.

NuGest 900™, <http://www.thehormoneshop.net/nugest900.htm>, (undated), 4 pages.

Panay, et al., "The 2013 British Menopause Society & Women's Health Concern Recommendations on Hormone Replacement Therapy," DOI: 0.1177/1754045313489645, [min.sagepub.com](http://min.sagepub.com). Menopause International: The Integrated Journal of Postreproductive Health 0(0):1-10, 2013.

Panchagnula et al., "Development and Evaluation of an Intracutaneous Depot Formulation of Corticosteroids Using Transcutol as a Cosolvent: In-Vitro, Ex-Vivo and In-Vivo Rat Studies," J Pharm Pharmacol. 43(9):609-614 (Sep. 1991). Abstract Only.

Patel, et al., "Transdermal Drug Delivery System: A Review," [www.thepharmajournal.com](http://www.thepharmajournal.com), vol. 1 No. 4 2012.

Salole, "The physiochemical properties of oestradiol," Journal of Pharmaceutical & Biomedical Analysis, 5 (7):635-648 (1987).

Sarrel, et al., "The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years," American Journal of Public Health, Published online ahead of print Jul. 18, 2013.

Shufelt, et al., "Hormone Therapy Dose, Formulation, Route of Delivery, and Risk of Cardiovascular Events in Women: Findings From the Women's Health Initiative Observational Study," Menopause: The Journal of the North American Menopause Society, vol. 21, No. 3, 2014.

Simon, et al., "Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet," The American College of Obstetricians and Gynecologists, vol. 112, No. 5, Nov. 2008.

Sitruk-Ware, et al., "Oral Micronized Progesterone," Department of Reproductive Endocrinology, vol. 36, No. 4, pp. 373-402, Oct. 1987.

Sitruk-Ware, et al., "Progestogens in Hormonal Replacement Therapy: New Molecules, Risks, and Benefits," Menopause: The Journal of the North American Menopause Society, vol. 9, No. 1, pp. 6-15, 2002.

Smith, et al., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens," JAMA Internal Medicine <http://archinte.jamanetwork.com>, Sep. 30, 2013.

Stanczyk, et al., "Ethinyl Estradiol and 17β-Estradiol in Combined Oral Contraceptives: Pharmacokinetics, Pharmacodynamics and Risk Assessment," Departments of Obstetrics and Gynecology and Preventive Medicine, University of Southern California Keck School of Medicine, Contraception 87 706-727, (2013).

Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," Pharmaceutical Research, 21(2):201-230 (Feb. 2004).

Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," Skin Pharmacol Physiol, 19:106-121 (2006). [http://www.nanobiotech.igmp.unicamp.br/download/Trommer\\_skin%20Openetration-2006rev.pdf](http://www.nanobiotech.igmp.unicamp.br/download/Trommer_skin%20Openetration-2006rev.pdf).

Whitehead, et al., "Absorption and Metabolism of Oral Progesterone," The British Medical Journal, vol. 280, No. 6217, Mar. 22, 1980.

Wood, et al., "Effects of Estradiol with Micronized Progesterone or Medroxyprogesterone Acetate on Risk Markers for Breast Cancer in Postmenopausal Monkeys," Springer Science+Business Media B.V., Breast Cancer Res Treat 101:125-134, (2007).

USPTO; Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545.

USPTO; Restriction/ Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562.

USPTO; Restriction/ Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623.

ABITEC Corporation, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.

Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.

Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.

Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.

Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.



## US 9,006,222 B2

Page 13

(56)

## References Cited

## OTHER PUBLICATIONS

- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," *Clinical Pharmacy*, 1990, vol. 9, No. 5, pp. 366-371.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," *Journal of Pharmaceutical Sciences*, vol. 86, No. 1, Jan. 1997, pp. 13-18.
- Sasol Olefins & Surfactants GmbH, Excipients for Pharmaceuticals, 2010, 28 pages.
- Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," *Food and Chemical Toxicology*, 72 (2014) pp. 40-50.
- Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," *Journal of Pharmaceutical Sciences*, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.
- ZRT Laboratory, Provider Data Sheet, About Dried Blood Spot Testing, 2014, 3 pages.
- Kubli-Garfias, C. et al., Ab initio calculations of the electronic structure of glucocorticoids, *Jour. of Mol. Structure, Theochem*, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, *Jour. of Mol. Structure, Theochem* vol. 425, pp. 171-179, 1998, Elsevier.
- Kuhnert-Brandstatter, M., Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , *Drug Development and Industrial Pharmacy*, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steroids, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G., et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , *Maturitas, The European Menopaus Journal*, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroidal conformation of 17a- and 17B-estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17b and Progesterone Concentrations in Uterine Lymph and Systematic Blood . . . , *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, *Catalent Pharma Solutions*, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MONO1500003758.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol.Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B- Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*, 35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://lxsr7.oru.edu/~alang/onsc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res*, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, *Crystal Structure Comm.*, Intn'l Union of Crystallography, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, *Schering Corporation*, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gisela L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012%20Patches\_Pack%20%28Estradiol/%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Salole, Eugene G., Estradiol, *Analytical Profiles of Drug Substances*, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Base . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, *SciFinder*, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.

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(56)

**References Cited**

**OTHER PUBLICATIONS**

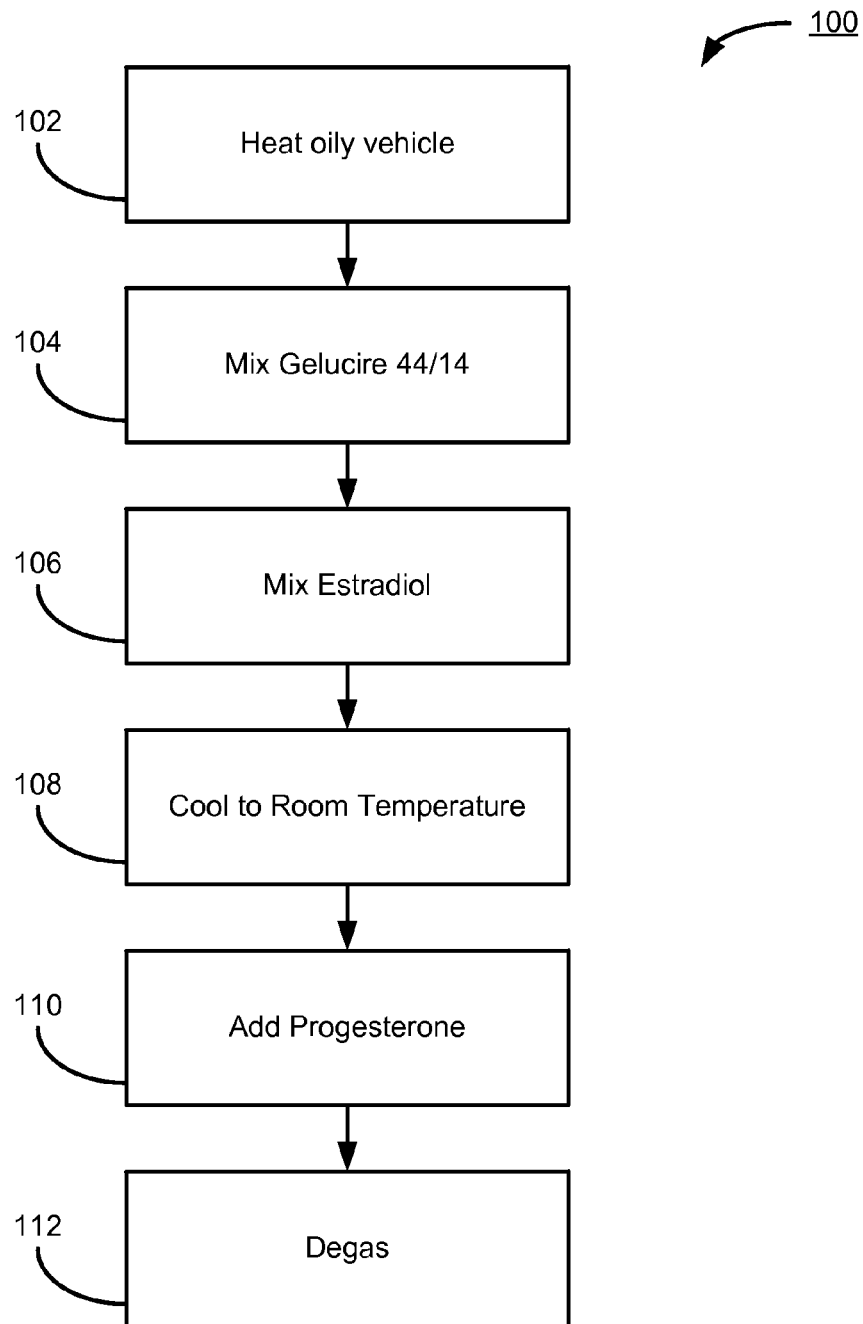
SciFinder Scholar Prednisone Chemical Properties, SciFinder, 2014, pp. 1-7, National Library of Medicine.  
SciFinder Scholar Prednisone Physical Properties, SciFinder, 2014, pp. 1-10, National Library of Medicine.  
SciFinder Scholar Progesterone Experimental Properties, SciFinder, pp. 1-9, Feb 24, 2014, American Chem. Society.

Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), Crystal Structure Comm., vol. 4(1) pp. 189-192, 1975, CAPLUS Database.

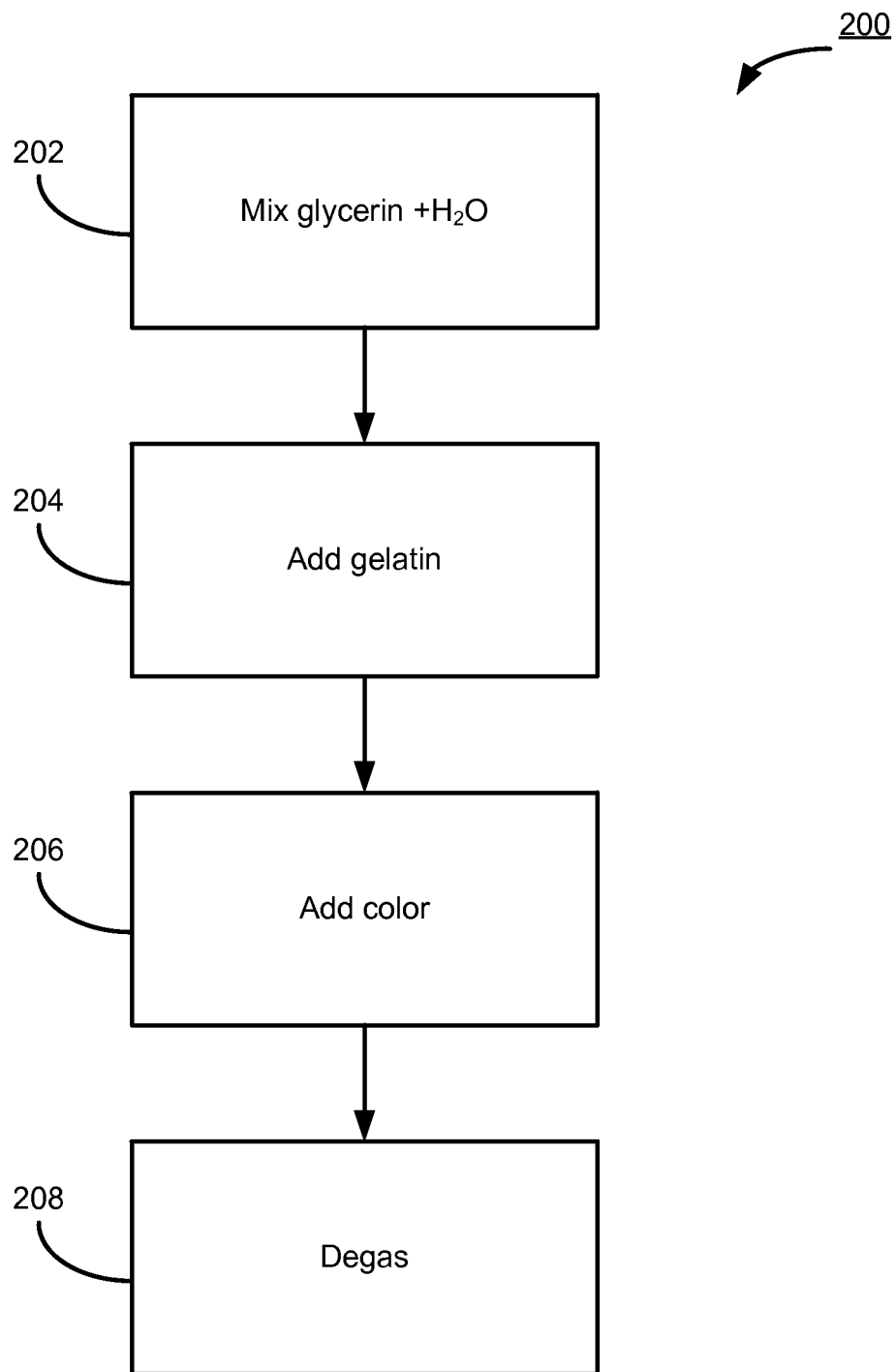
Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.

Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>.

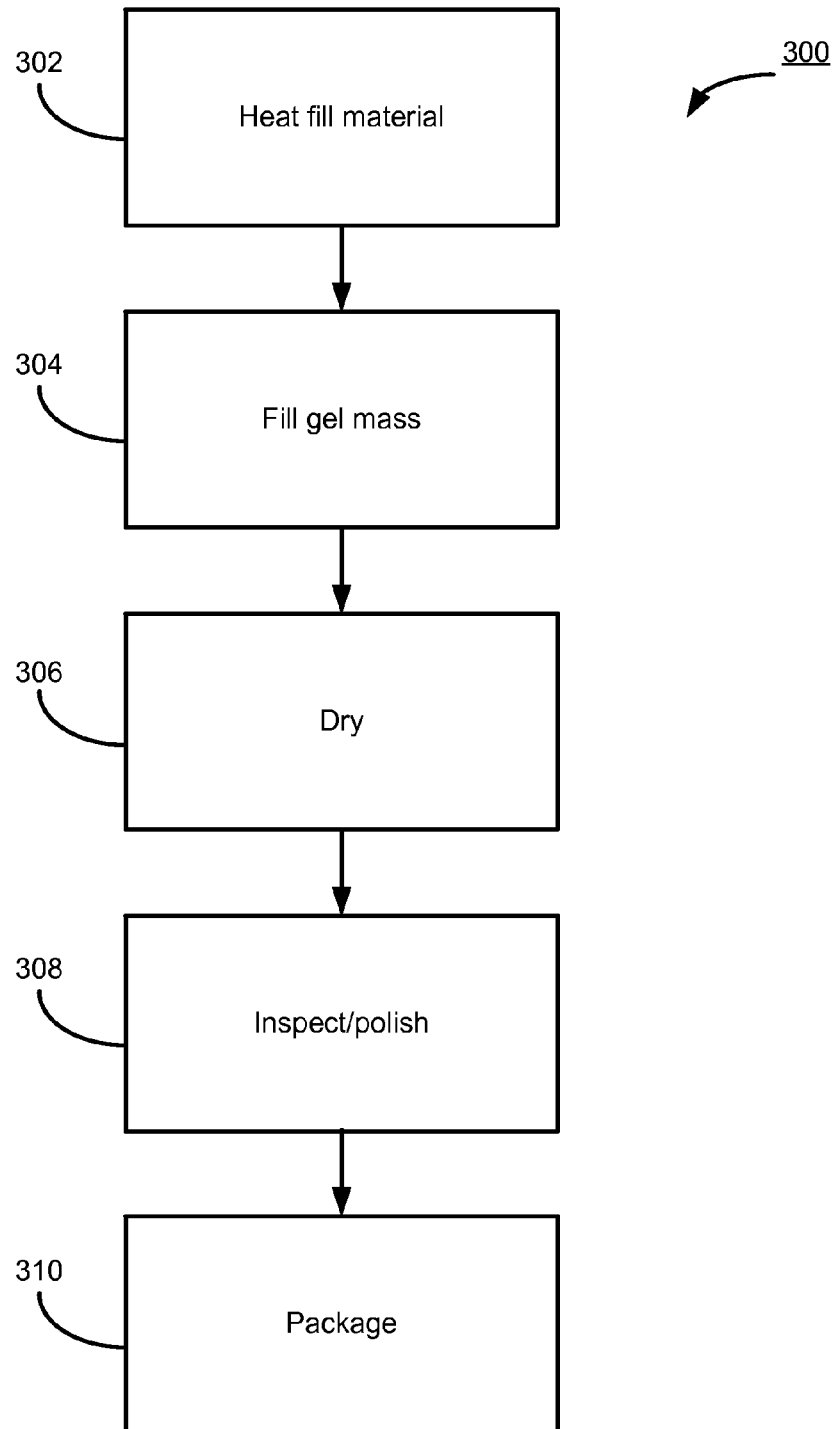




**FIG. 1**



**FIG. 2**



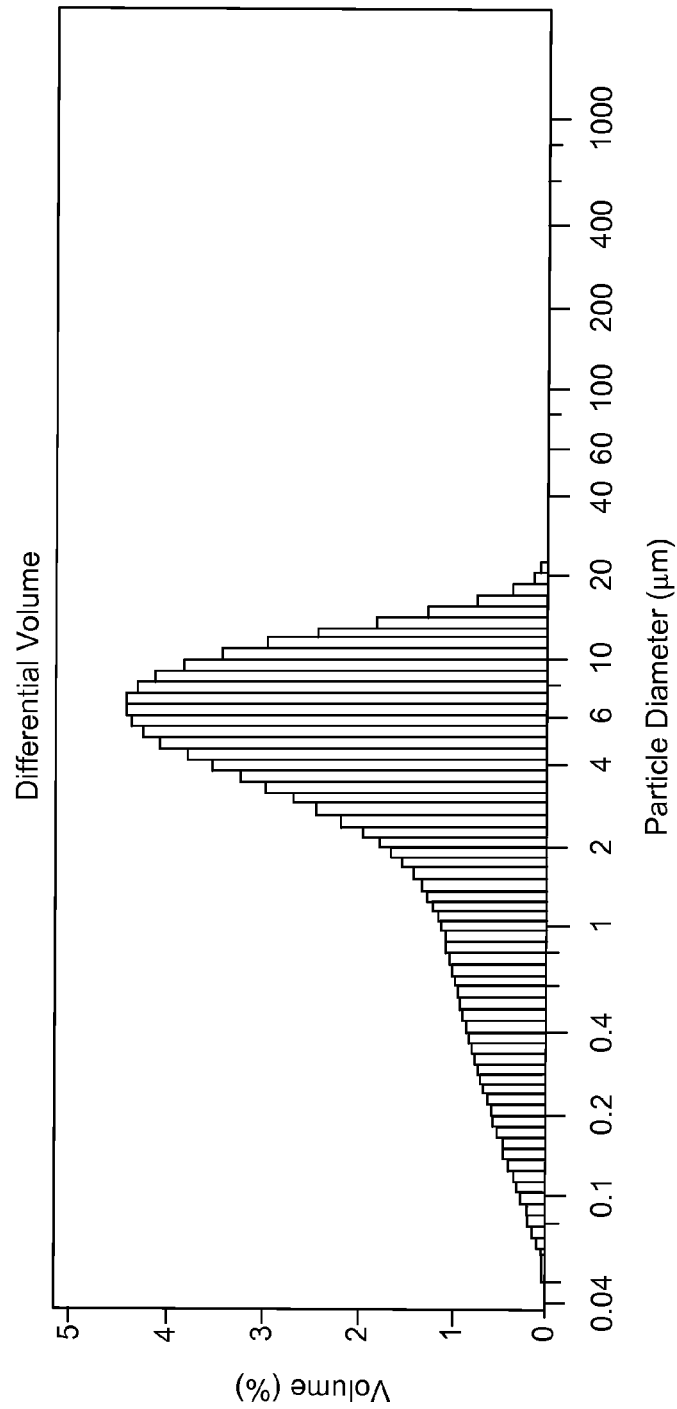
**FIG. 3**

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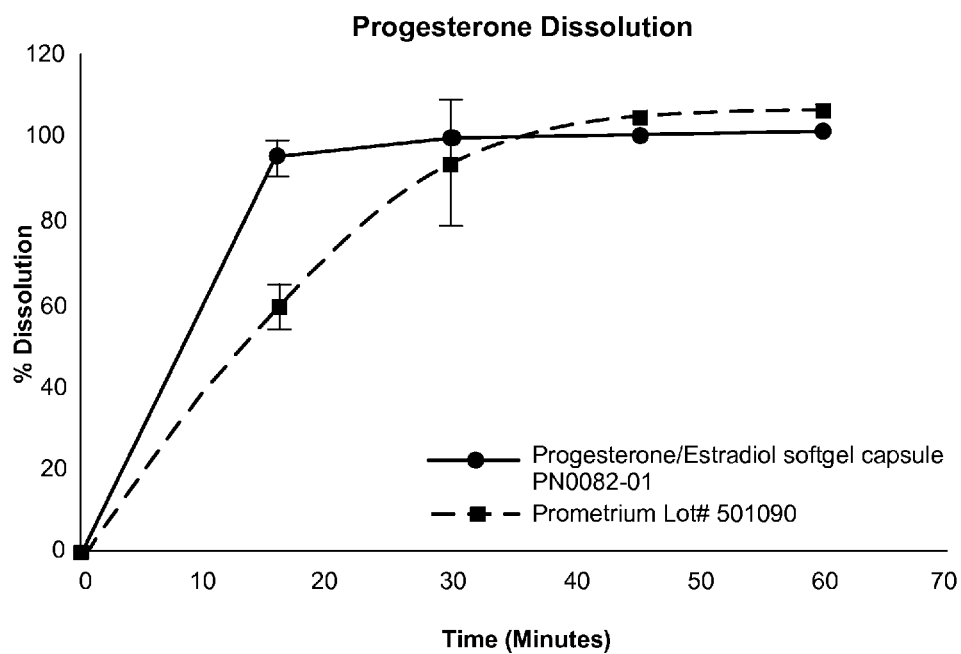
**FIG. 4**

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**FIG. 5**

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# **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

## **CROSS REFERENCE TO RELATED APPLICATIONS**

This application claims priority to the following U.S. Patent Applications: U.S. application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES," which was filed on Nov. 21, 2012; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULA- TIONS," which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

## **BACKGROUND**

### **1. Field**

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

### **2. Discussion of the Related Art**

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bod-

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ies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Prometrium was approved for sale in the United States on May 14, 1998 under NDA #N019781. According to the prescribing information approved for this product (Rev June 2009) ("Prometrium prescribing information"), Prometrium comprises synthetic progesterone that is chemically identical to progesterone of human ovarian origin. Capsules comprise 100 mg or 200 mg of micronized progesterone. The inactive ingredients include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, and yellow and red dyes.

Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

## **SUMMARY**

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

## **BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES**

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.



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FIG. 5 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

#### DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

#### Definitions

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, Cmax, and optionally, Tmax.

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “Cmax” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “Tmax” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, Cmax and, optionally, Tmax are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal especially a mammal, including human, subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without

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limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, such as an organic oil other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution, i.e., at least 98% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%, i.e., up to but not including 98% in solution.

As used herein, unless specified, estradiol includes estradiol in anhydrous and hemihydrate forms.

#### DESCRIPTION

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be

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desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %; estradiol is 0.1 to 0.8 wt %, e.g., 0.15 to 0.35 wt %.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

According to the Prometrium prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered Prometrium once a day for five days resulted in the mean PK parameters listed in the following table:

Parameter	Prometrium Capsules Daily Dose		
	100 mg	200 mg	300 mg
$C_{max}$ (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
$T_{max}$ (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
$AUC_{0-10}$ (ng x hr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

In a particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions

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treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 $\beta$ -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017  $\mu$ m to 2000  $\mu$ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing

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zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4  $\mu\text{m}$  to 2000  $\mu\text{m}$ . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of caproic fatty acid; caprylic fatty acid; capric fatty acid; tauric acid; myristic acid; linoleic acid; succinic acid; glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: Transcutol); diethylene glycol monoethyl ether; esters of saturated

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coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Capmul MCM; Capmul MCM and a non-ionic surfactant; and Capmul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant, e.g., Gelucire 44/14, can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, Capmul MCM and Gelucire were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. See, e.g., Tables 13-17, below. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In illustrative embodiments of the invention, oils used to solubilize estradiol and to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, estradiol or progesterone (or both) is soluble in the oils at room temperature, although it may be desirable to warm the oils up until they are in a liquid state. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50 C, e.g., at or below 50 C, at or below 40 C, or at or below 50 C. In illustrative embodiments, Gelucire 44/14 is heated to about 65 C and Capmul MCM is heated to about 40 C to facilitate mixing of the oil and non-surfactant, although such heating is not necessary to dissolve the estradiol or progesterone. In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8 wt % or higher, or 1.0 wt % or higher.

Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, Capmul MCM, Capmul MCM C10, Capmul MCM C8, and Capmul MCM C8 EP. These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, Miglyol 810 and Miglyol 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, Capmul PG-8, Capmul PG-2L EP/NF, Capmul PG-8 NF, Capmul PG-12 EP/NF and Capryol. Other illustrative examples include Miglyol 840.

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others,



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Gelucire 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol. Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of Gelucire, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids. Specifically, a product information sheet for Myglyol by SASOL provides as the composition of fatty acids as follows:

Tests	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic acid (C14:0)	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

It will be understood that oils are often mixtures. So, for example, when an oil is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for Capmul MCM C8 describes Capmul MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher,

Mixtures of medium chain fatty acid glycerides, e.g., C6-C12, C8-C12, or C8-C10 fatty acid mono- and diglycerides or mono-, di-, and triglycerides are very well suited for dissolving estradiol; good results have been obtained with an oil that is predominantly a mixture of C8-C10 saturated fatty acid mono- and diglycerides. Longer chain glycerides appear to be not as well suited for dissolution of estradiol. On the other hand, high solubility of progesterone has been obtained in mixtures that are predominantly medium chain fatty acid triglycerides.

High solubility of estradiol has been obtained in 2-(2-Ethoxyethoxy)ethanol, e.g., Transcutol and in Propylene glycol monocaprylate, e.g., Capryol™ 90 (Gattefosse).

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone or estradiol. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., Capmul MCM) and polyethylene glycol glycerides (e.g., Gelucire) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65 C in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature or at lower temperatures as the mixture cools or even after it has cooled as temperatures above room temperature, e.g., about 20 C, are not required to solubilize the estradiol in preferred oils. The progesterone can also be added as the mixture cools, e.g., to below about 40 C or to below about 30 C, even down to room temperature.

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In various embodiments, estradiol is solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid esters or alcohols. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, Gelucire 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, e.g., Tables 13-17, below. Other non-ionic surfactants include, e.g., Labrasol® PEG-8 Caprylic/Capric Glycerides (Gattefosse) and Labarafil® corn/apricot oil PEG-6 esters (Gattefosse).

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

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As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises solubilized estradiol, progesterone at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of glycerol, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with Gelucire as surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following four formulations:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Formulation A- P: 50/EE: 0.25:		
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.17	0.26
Capmul MCM, NF	65.49	98.24
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00
Formulation B- P: 50/EE: 0.5:		
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.35	0.52
Capmul MCM, NF	65.32	97.98
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00
Formulation C - P: 100/EE: 0.5:		
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.17	0.52
Capmul MCM, NF	65.49	196.48
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00
Formulation D - P: 100/EE: 1:		
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.34	1.03
Capmul MCM, NF	65.32	195.97
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00
Formulation E- P: 200/EE: 2:		
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate	0.34	2.06
Capmul MCM, NF	65.32	391.94
Gelucire 44/14, NF	1.00	6.00
Total	100.00	600.00

\*Note:

1.00 mg Estradiol equivalent to 1.03 mg Estradiol Hemihydrate.

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In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono- and diglycerides, such as Capmul MCM, and 0.5 to 10 wt % non-ionic surfactant, such as Gelucire 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opatint red and white, and, optionally, Miglyol 812.

Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g., 75%, 80%, 85%, 90%, or >95%, is solubilized appear to provide improved PK-related properties.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use;

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reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

## EXAMPLES

## Example 1

## Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

\*Literature reference -Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

In further solubility studies, estradiol was soluble at at least 6 mg/gm Miglyol Transcutol in ratios of 81:19 to 95:5, in Miglyol; ethanol at 91:11, and in Miglyol:Capmul PG8 at 88:11, but not in Miglyol:Transcutol at 96:4, Miglyol:Labra-sol at 70:30 to 80:20, or Miglyol:Capmul PG8 at 86:14.

## Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60

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TABLE 2-continued

Ingredient	Solubility (mg/g)
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

## Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol: Miglyol: Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

## Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.



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TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

## Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/ Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

## Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/ Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

## Example 7

## Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the

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solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

## Example 7-1

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

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TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, Campul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/-2° C. Gelucire 44/14 may be added to the Campul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Campul MCM.

Heat may be removed from the Gelucire 44/14 and Campul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Campul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

## Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

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TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 4.

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## Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0  $\mu$ m, an X75 of 17.3  $\mu$ m, and an X25 of 5.3  $\mu$ m. The Beckman Device also yielded that the mean particle size is 11.8  $\mu$ m, the median particle size is 11.04  $\mu$ m, the mode particle size is 13.6  $\mu$ m, and the standard deviation is 7.8  $\mu$ m.

## Example 12

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is heated to 65 C and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

## Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:			100.000	200.00 mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

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TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation. Alternatively, Gelucire 44/14 is heated to 65 C and Capmul MCM is heated to 40 C +/-5 C to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 40 C; the mixture is then passed through a colloid mill, e.g., three times.

## Example 15

Study 352—Progesterone and Estradiol Combination Study under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	7.14	50.00
Estradiol Hemihydrate, USP Micronized	0.30	2.07
Capmul MCM, NF, USP	83.27	582.93
Gelucire 44/14, NF	9.29	650
Total	100.00	700

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

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Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ± 20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters C<sub>max</sub>, AUC<sub>0-t</sub> & AUC<sub>0-∞</sub> were calculated on data obtained from 24 subjects for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

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Corrected pharmacokinetic profile summaries are presented in Table 18, below, for progesterone.

TABLE 18

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C <sub>max</sub>	47.0	43.0	81.0 ± 82.8	117.7 ± 173.7
AUC <sub>0-t</sub>	107.6	97.8	163.9 ± 136.5	191.1 ± 241.7
AUC <sub>0-∞</sub>	110.7	110.0	173.5 ± 143.0	207.1 ± 250.3

\*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters C<sub>max</sub>, AUC<sub>0-t</sub> & AUC<sub>0-∞</sub> were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 19, below for progesterone.

TABLE 19

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C <sub>max</sub>	2.3	3.0	2.9 ± 2.3	3.9 ± 3.4
AUC <sub>0-t</sub>	8.4	10.9	11.2 ± 8.7	14.5 ± 11.0
AUC <sub>0-∞</sub>	12.9	17.2	15.1 ± 9.0	19.6 ± 10.2

\*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to Prometrium.

## Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ± 5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.



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Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C. +/−3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C. +/−10° C. The wedge temperature may be 38° C. +/−3° C. The drum cooling temperature may be 4° C. +/−2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about

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120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

## Example 17

## Solubility of Estradiol in Soy Bean Oil, Peanut Oil, and Safflower Oil

Data was obtained visually by making the mixtures described below, sonicating the mixtures, and then seeing if a clear solution resulted. If a clear solution was achieved, it was an indication of solubility at the level studied.

## Procedures and Results:

## Step 1.

0.3% of Estradiol suspension in each oil was prepared by adding 30 mg Estradiol to solvent and QS to 10 g. Samples were mixed on vortex for 2 hours, heated @ 50° C. for 30 minutes and then mixed for 1 hour more. All samples were still in suspension form.

## Step 2.

Each sample was diluted to 0.24% (by adding 2.5 g more oil) and mixed for 2 hours and heated @50° C. for 30 min and mixed again for one hour. All the samples were still cloudy. Samples were kept at room temperature overnight to see if they precipitate or if un-dissolved API settles out. After 20 hours at room temperature, it was observed that all samples still had un-dissolved API.

## Step 3.

Each sample was diluted to 0.2% (by adding 2.5 g more oil) and mixed 2 for hours and heated @50° C. for 30 min and mixed again for one hour. All the samples were still slightly cloudy, indicating that the estradiol was not completely dissolved.

TABLE 20

Ingredient	Estradiol Solubility (mg/g)	Estradiol Solubility (% w/w)
Peanut Oil	<2	<0.2
Safflower Oil	<2	<0.2
Soy Bean Oil	<2	<0.2

The solubility of estradiol in all three oils was less than 2 mg/g (0.2% w/w). This level of solubility is significantly below the solubility that the present inventors have discovered can be achieved in other oils, e.g., medium chain fatty acid esters, such as the mono/diglycerides, propylene glycol esters, and polyethylene glycol esters discussed above.

In sum, if no heat is used to dissolve estradiol in safflower oil, it will not go into solution. Given that the estradiol did not dissolve at 50 C, oils such as safflower oil will not be useful in the methods of the invention using medium chain fatty acid esters as described hereinabove.

## Example 18

## Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of Prometrium and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second

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study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37 C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from Prometrium. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from Prometrium is attached as FIG. 5.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

We claim:

1. A pharmaceutical composition comprising:

a solubilizing agent, the solubilizing agent comprising an effective amount of a C6-C12 oil;

1.0 mg estradiol or 1.03 mg estradiol hemihydrate, the estradiol or estradiol hemihydrate being at least about 90% solubilized in the solubilizing agent; and

100 mg progesterone;

wherein the estradiol or the estradiol hemihydrate, and the progesterone are uniformly dispersed in the solubilizing agent.

2. The pharmaceutical composition of claim 1, wherein the solubilizing agent is selected from at least one of monoglycerides, diglycerides, triglycerides, and combinations thereof, wherein the monoglycerides, diglycerides, and triglycerides are predominantly of C6-C12 fatty acid chain lengths.

3. The pharmaceutical composition of claim 2, wherein the monoglycerides, diglycerides, and triglycerides are >50% C6-C12 fatty acid chain lengths.

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4. A pharmaceutical composition comprising:

about 100 mg progesterone;

about 1.0 mg estradiol or 1.03 mg estradiol hemihydrate, the estradiol or estradiol hemihydrate being at least about 90% solubilized;

about 195.97 mg of monoglycerides and diglycerides of caprylic acid and capric acid (CAPMUL MCM); and about 3.0 mg of at least one of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, or lauroyl polyoxylglycerides (GELUCIRE 44/14);

wherein the estradiol or the estradiol hemihydrate, and the progesterone are uniformly dispersed in the solubilizing agent.

5. A method of treating a menopause-related symptom in a woman comprising administering an effective amount of pharmaceutical composition to a subject in need thereof, the pharmaceutical composition comprising:

about 100 mg progesterone;

about 1.0 mg estradiol or 1.03 mg estradiol hemihydrate, the estradiol or estradiol hemihydrate being at least about 90% solubilized;

about 195.97 mg of monoglycerides and diglycerides of caprylic acid and capric acid (CAPMUL MCM); and about 3.0 mg of at least one of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, or lauroyl polyoxylglycerides (GELUCIRE 44/14);

wherein the estradiol or the estradiol hemihydrate, and the progesterone are uniformly dispersed in the solubilizing agent.

6. The method of claim 5, wherein the pharmaceutical composition is administered as a continuous-combined therapy regimen.

7. The method of claim 5, wherein the pharmaceutical composition is administered a sequentially-combined therapy regimen.

8. A method of treating a vasomotor symptom in a woman comprising administering an effective amount of a pharmaceutical composition comprising:

1.0 mg estradiol or 1.03 mg estradiol hemihydrate, the estradiol or estradiol hemihydrate being at least about 90% solubilized in the solubilizing agent;

100 mg progesterone; and

a solubilizing agent, the solubilizing agent comprising an effective amount of a C6-C12 oil;

wherein the estradiol or the estradiol hemihydrate, and the progesterone are uniformly dispersed in the solubilizing agent; and

wherein the pharmaceutical composition is administered once daily for the treatment of symptoms associated with menopause.

9. The method of claim 8, wherein the pharmaceutical composition is administered as a continuous-combined therapy regimen.

10. The method of claim 8, wherein the pharmaceutical composition is administered as a sequentially-combined therapy regimen.

11. The method of claim 8, wherein the solubilizing agent is selected from at least one of monoglycerides, diglycerides, triglycerides, and combinations thereof, wherein the monoglycerides, diglycerides, and triglycerides are predominantly of C6-C12 fatty acid chain lengths.

12. The method of claim 11, wherein the monoglycerides, diglycerides, and triglycerides are >50% C6-C12 fatty acid chain lengths.

\* \* \* \* \*



UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 9,006,222 B2  
APPLICATION NO. : 14/099623  
DATED : April 14, 2015  
INVENTOR(S) : Brian A. Bernick et al.

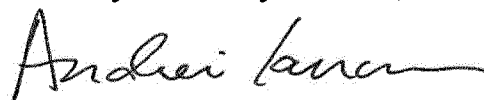
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this  
Twenty-fifth Day of June, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu  
*Director of the United States Patent and Trademark Office*

# EXHIBIT H



US009114145B2

(12) **United States Patent**  
**Bernick et al.**

(10) **Patent No.: US 9,114,145 B2**  
(45) **Date of Patent: \*Aug. 25, 2015**

(54) **NATURAL COMBINATION HORMONE  
REPLACEMENT FORMULATIONS AND  
THERAPIES**

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(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-  
claimer.

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(60) Continuation of application No. 14/099,545, filed on  
Dec. 6, 2013, now Pat. No. 8,846,648, which is a  
division of application No. 13/684,002, filed on Nov.  
21, 2012, now Pat. No. 8,633,178.

(60) Provisional application No. 61/662,265, filed on Jun.  
20, 2012, provisional application No. 61/661,302,  
filed on Jun. 18, 2012, provisional application No.  
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(51) **Int. Cl.**

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(56) **References Cited**

**U.S. PATENT DOCUMENTS**

2,232,438 A 2/1941 Butenandt  
4,900,734 A \* 2/1990 Maxson et al. .... 514/171  
5,538,736 A 7/1996 Hoffmann et al.  
5,556,635 A 9/1996 Istin et al.

5,580,572 A 12/1996 Mikler et al.  
5,605,702 A 2/1997 Teillaud et al.  
5,607,691 A 3/1997 Hale et al.  
5,607,693 A 3/1997 Bonte et al.  
5,609,617 A 3/1997 Shealy et al.  
5,626,866 A 5/1997 Ebert et al.  
5,653,983 A 8/1997 Meybeck et al.  
5,660,839 A 8/1997 Allec et al.  
5,662,927 A 9/1997 Ehrlich et al.  
5,663,160 A 9/1997 Meybeck et al.  
5,686,097 A 11/1997 Taskovich et al.  
5,693,335 A 12/1997 Xia et al.  
5,700,480 A 12/1997 Hille et al.  
5,719,197 A 2/1998 Kanios et al.  
5,770,220 A 6/1998 Meconi et al.  
5,770,227 A 6/1998 Dong et al.  
5,780,044 A 7/1998 Yewey et al.  
5,780,050 A 7/1998 Jain et al.  
5,788,984 A 8/1998 Guenther et al.  
5,820,878 A 10/1998 Hirano et al.  
5,840,327 A 11/1998 Gale et al.  
5,843,468 A 12/1998 Burkoth et al.  
5,843,979 A 12/1998 Wille et al.  
5,858,394 A 1/1999 Lipp et al.  
5,863,552 A 1/1999 Yue  
5,882,676 A 3/1999 Lee et al.  
5,885,612 A 3/1999 Meconi et al.  
5,888,533 A 3/1999 Dunn

(Continued)

**FOREIGN PATENT DOCUMENTS**

WO WO9619975 7/1996  
WO WO0241878 5/2002  
WO WO03028667 4/2003  
WO WO2004014432 2/2004  
WO WO2005081825 9/2005  
WO WO2007120868 10/2007  
WO WO2010146872 12/2010  
WO WO2012055814 A1 5/2012  
WO WO2012055840 A1 5/2012  
WO WO2012065740 5/2012

(Continued)

**OTHER PUBLICATIONS**

Abitec Corporation, Excipients for the Pharmaceutical Industry—  
Regulatory and Product Information, 2013, 2 pages.

(Continued)

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(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are pro-  
vided herein. Among others, the following formulations are  
provided herein: solubilized estradiol without progesterone;  
micronized progesterone without estradiol; micronized  
progesterone with partially solubilized progesterone; solu-  
bilized estradiol with micronized progesterone; solubilized  
estradiol with micronized progesterone in combination with  
partially solubilized progesterone; and solubilized estradiol  
with solubilized progesterone.

**18 Claims, 4 Drawing Sheets**

## US 9,114,145 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

5,891,462	A	4/1999	Carrara	7,153,522	B1	12/2006	Ikeura et al.
5,902,603	A	5/1999	Chen et al.	7,175,850	B2	2/2007	Cevc
5,904,931	A	5/1999	Lipp et al.	7,198,800	B1	4/2007	Ko
5,906,830	A	5/1999	Farinas et al.	7,381,427	B2	6/2008	Ancira et al.
5,912,010	A	6/1999	Wille et al.	7,456,159	B2	11/2008	Houze et al.
5,919,477	A	7/1999	Bevan et al.	7,498,303	B2	3/2009	Arnold et al.
5,942,243	A	8/1999	Shah	7,534,780	B2	5/2009	Wyrwa et al.
5,952,000	A	9/1999	Venkateshwaran et al.	7,569,274	B2	8/2009	Besse et al.
5,968,919	A	10/1999	Samour et al.	7,799,769	B2	9/2010	White et al.
5,985,311	A	11/1999	Cordes et al.	7,815,936	B2	10/2010	Hasenzahl et al.
5,985,850	A	11/1999	Falk et al.	7,829,116	B2	11/2010	Griswold et al.
5,989,568	A	11/1999	Breton et al.	7,850,992	B2	12/2010	Kim et al.
6,007,835	A	12/1999	Bon Lapillonne et al.	7,854,753	B2	12/2010	Kraft et al.
6,010,715	A	1/2000	Wick et al.	7,871,643	B2	1/2011	Lizio et al.
6,013,276	A	1/2000	Math et al.	7,960,368	B2	6/2011	Nickisch et al.
6,024,974	A	2/2000	Li	8,048,017	B2	11/2011	Xu
6,030,948	A	2/2000	Mann	8,063,030	B2	11/2011	Ellman
6,040,340	A	3/2000	Chwalisz et al.	8,071,576	B2	12/2011	Coelingh Bennink et al.
6,068,853	A	5/2000	Giannos et al.	8,075,916	B2	12/2011	Song et al.
6,087,352	A	7/2000	Trout	8,075,917	B2	12/2011	Chung et al.
6,090,404	A	7/2000	Meconi et al.	8,076,317	B2	12/2011	Kulmann
6,106,848	A	8/2000	Preuilh et al.	8,080,553	B2	12/2011	Keith et al.
6,124,362	A	9/2000	Bradbury et al.	8,096,940	B2	1/2012	Josephson et al.
6,139,868	A	10/2000	Hoffmann	8,114,152	B2	2/2012	Furst
6,149,935	A	11/2000	Chiang et al.	8,114,442	B2	2/2012	Tucker et al.
6,187,323	B1	2/2001	Aiache et al.	8,119,741	B2	2/2012	Pavlin
6,217,886	B1	4/2001	Onyuksel et al.	8,124,118	B2	2/2012	Lennernaes et al.
6,225,297	B1	5/2001	Stockemann et al.	8,124,595	B2	2/2012	Boissonneault
6,228,383	B1	5/2001	Hansen et al.	8,147,561	B2	4/2012	Binmoeller
6,228,852	B1	5/2001	Shaak	8,148,546	B2	4/2012	Schuster et al.
6,242,509	B1	6/2001	Berger et al.	8,158,613	B2	4/2012	Staniforth et al.
6,245,811	B1	6/2001	Horrobin et al.	8,163,722	B2	4/2012	Savoir et al.
6,267,984	B1	7/2001	Beste et al.	8,177,449	B2	5/2012	Bayly et al.
6,274,165	B1	8/2001	Meconi et al.	8,187,615	B2	5/2012	Friedman
6,303,132	B1	10/2001	Nelson	8,195,403	B2	6/2012	Ishikawa et al.
6,303,588	B1	10/2001	Danielov	8,221,785	B2	7/2012	Chien
6,312,703	B1	11/2001	Orthofer	8,222,237	B2	7/2012	Nickisch et al.
6,328,987	B1	12/2001	Marini	8,257,724	B2	9/2012	Cromack et al.
6,344,211	B1	2/2002	Hille	8,257,725	B2	9/2012	Cromack et al.
6,372,245	B1	4/2002	Bowman et al.	8,268,352	B2	9/2012	Vaya et al.
6,420,352	B1	7/2002	Knowles	8,268,806	B2	9/2012	Labrie
6,432,438	B1	8/2002	Shukla	8,268,878	B2	9/2012	Armer et al.
6,451,300	B1	9/2002	Dunlop et al.	8,288,366	B2	10/2012	Chochinov et al.
6,465,004	B1	10/2002	Rossi Montero et al.	8,318,898	B2	11/2012	Fasel et al.
6,465,005	B1	10/2002	Biali et al.	8,324,193	B2	12/2012	Lee-Sepsick et al.
6,465,006	B1	10/2002	Zhang et al.	8,337,814	B2	12/2012	Osbakken et al.
6,495,160	B2	12/2002	Esposito et al.	8,344,007	B2	1/2013	Tang et al.
6,521,250	B2	2/2003	Meconi et al.	8,353,863	B2	1/2013	Imran
6,531,149	B1	3/2003	Kirstgen et al.	8,357,723	B2	1/2013	Satyam
6,538,039	B2	3/2003	Laurent	8,361,995	B2	1/2013	Schramm
6,548,053	B1	4/2003	Stewart et al.	8,362,091	B2	1/2013	Tamarkin et al.
6,555,131	B1	4/2003	Wolff et al.	8,372,424	B2	2/2013	Berry et al.
6,562,367	B1	5/2003	Wolff et al.	8,372,806	B2	2/2013	Boehler et al.
6,562,370	B2	5/2003	Luo et al.	8,377,482	B2	2/2013	Laurie et al.
6,562,790	B2	5/2003	Chein	8,377,994	B2	2/2013	Gray et al.
6,599,519	B1	7/2003	Seo et al.	8,394,759	B2	3/2013	Barathur et al.
6,610,674	B1	8/2003	Schreiber	8,415,332	B2	4/2013	Diliberti et al.
6,635,274	B1	10/2003	Masiz et al.	8,435,972	B2	5/2013	Stein et al.
6,638,528	B1	10/2003	Kanios	8,449,879	B2	5/2013	Laurent Applegate et al.
6,649,155	B1	11/2003	Dunlop et al.	8,450,108	B2	5/2013	Boyce
6,682,757	B1	1/2004	Wright	8,454,945	B2	6/2013	McCook et al.
6,708,822	B1	3/2004	Muni	8,455,468	B2	6/2013	Hoffman et al.
6,720,001	B2	4/2004	Chen et al.	8,461,138	B2	6/2013	Boissonneault
6,743,448	B2	6/2004	Kryger	8,476,252	B2	7/2013	Achleitner et al.
6,750,291	B2	6/2004	Kim et al.	8,481,488	B2	7/2013	Carter
6,821,524	B2	11/2004	Marini	8,486,374	B2	7/2013	Tamarkin et al.
6,911,211	B2	6/2005	Eini et al.	8,486,442	B2	7/2013	Matsushita et al.
6,960,337	B2	11/2005	Daniels et al.	8,492,368	B2	7/2013	Vanlandingham et al.
6,974,569	B2	12/2005	Dunlop et al.	8,507,467	B2	8/2013	Matsui et al.
6,995,149	B1	2/2006	Endrikat et al.	8,512,693	B2	8/2013	Capito et al.
7,004,321	B1	2/2006	Palm et al.	8,512,754	B2	8/2013	Needham
7,030,104	B2	4/2006	Gray et al.	8,518,376	B2	8/2013	Tamarkin et al.
7,094,228	B2	8/2006	Zhang et al.	8,536,159	B2	9/2013	Li et al.
7,097,853	B1	8/2006	Garbe et al.	8,540,967	B2	9/2013	Barrett et al.
7,105,573	B2	9/2006	Krajcik et al.	8,541,400	B2	9/2013	Johnsson et al.
				8,551,462	B2	10/2013	Goldstein et al.
				8,557,281	B2	10/2013	Halliday et al.
				8,568,374	B2	10/2013	De Graaff et al.
				8,591,951	B2	11/2013	Kohn et al.

## US 9,114,145 B2

Page 3

(56)	<b>References Cited</b>					
	U.S. PATENT DOCUMENTS					
	8,613,951 B2	12/2013	Zale et al.	2005/0239747 A1	10/2005	Yang et al.
	8,633,178 B2	1/2014	Bernick et al.	2005/0239758 A1	10/2005	Roby
	8,633,180 B2	1/2014	Li et al.	2005/0244360 A1	11/2005	Billoni
	8,636,787 B2	1/2014	Sabaria	2005/0266088 A1	12/2005	Hinrichs et al.
	8,636,982 B2	1/2014	Tamarkin et al.	2005/0271597 A1	12/2005	Keith
	8,653,129 B2	2/2014	Fein et al.	2005/0272685 A1	12/2005	Hung
	8,658,627 B2	2/2014	Voskuhl	2006/0009428 A1	1/2006	Grubb et al.
	8,663,692 B1	3/2014	Mueller et al.	2006/0034904 A1	2/2006	Weimann
	8,663,703 B2	3/2014	Lerner et al.	2006/0078618 A1	4/2006	Constantinides et al.
	8,664,207 B2	3/2014	Li et al.	2006/0084704 A1	4/2006	Shih et al.
	8,669,293 B2	3/2014	Levy et al.	2006/0088580 A1	4/2006	Meconi et al.
	8,679,552 B2	3/2014	Guthery	2006/0100180 A1	5/2006	Nubbemeyer et al.
	8,697,127 B2	4/2014	Sah	2006/0121102 A1	6/2006	Chiang
	8,697,710 B2	4/2014	Li et al.	2006/0165744 A1	7/2006	Jamil et al.
	8,703,105 B2	4/2014	Tamarkin et al.	2006/0193789 A1	8/2006	Tamarkin et al.
	8,709,385 B2	4/2014	Tamarkin et al.	2006/0233743 A1	10/2006	Kelly
	8,709,451 B2	4/2014	Nam et al.	2006/0233841 A1	10/2006	Brodbeck et al.
	8,715,735 B2	5/2014	Funke et al.	2006/0246122 A1	11/2006	Langguth et al.
	8,721,331 B2	5/2014	Raghuprasad	2006/0247221 A1	11/2006	Coelingh Bennink et al.
	8,722,021 B2	5/2014	Friedman et al.	2006/0251581 A1	11/2006	McIntyre et al.
	8,734,846 B2	5/2014	Ali et al.	2006/0275218 A1	12/2006	Tamarkin et al.
	8,735,381 B2	5/2014	Podolski	2006/0276414 A1	12/2006	Coelingh Bennink et al.
	8,741,336 B2	6/2014	Dipierro et al.	2006/0292223 A1	12/2006	Woolfson et al.
	8,741,373 B2	6/2014	Bromley et al.	2007/0009559 A1	1/2007	Li et al.
	8,753,661 B2	6/2014	Steinmuller Nethl et al.	2007/0009594 A1	1/2007	Grubb et al.
	8,784,882 B2	7/2014	Mattern	2007/0010550 A1	1/2007	McKenzie
	2001/0009673 A1	7/2001	Lipp et al.	2007/0014839 A1	1/2007	Bracht
	2001/0023261 A1	9/2001	Ryoo et al.	2007/0015698 A1	1/2007	Kleinman et al.
	2001/0053383 A1	12/2001	Miranda et al.	2007/0037780 A1	2/2007	Ebert et al.
	2002/0035070 A1	3/2002	Gardlik et al.	2007/0037782 A1	2/2007	Hibino et al.
	2002/0119174 A1	8/2002	Gardlik et al.	2007/0078091 A1	4/2007	Hubler et al.
	2002/0119198 A1	8/2002	Gao et al.	2007/0128263 A1	6/2007	Gargiulo et al.
	2002/0142017 A1	10/2002	Simonnet	2007/0154533 A1	7/2007	Dudley
	2002/0169205 A1	11/2002	Chwalisz et al.	2007/0167418 A1	7/2007	Ferguson
	2002/0193758 A1	12/2002	Sandberg	2007/0185068 A1	8/2007	Ferguson et al.
	2002/0197286 A1	12/2002	Brandman et al.	2007/0190022 A1	8/2007	Bacopoulos et al.
	2003/0003139 A1	1/2003	Lipp et al.	2007/0196415 A1	8/2007	Chen et al.
	2003/0027772 A1	2/2003	Breton	2007/0232574 A1	10/2007	Galey et al.
	2003/0044453 A1	3/2003	Dittgen et al.	2007/0248658 A1	10/2007	Zurdo Schroeder et al.
	2003/0091620 A1	5/2003	Fikstad et al.	2007/0254858 A1	11/2007	Cronk
	2003/0109507 A1	6/2003	Franke et al.	2007/0255197 A1	11/2007	Humberstone et al.
	2003/0113268 A1	6/2003	Buenafoe et al.	2007/0287688 A1	12/2007	Chan et al.
	2003/0170295 A1	9/2003	Kim et al.	2007/0292359 A1	12/2007	Friedman et al.
	2003/0175329 A1	9/2003	Azarnoff et al.	2007/0292461 A1	12/2007	Tamarkin et al.
	2003/0175333 A1	9/2003	Shefer et al.	2007/0292493 A1	12/2007	Brierre
	2003/0219402 A1	11/2003	Rutter	2007/0298089 A1	12/2007	Saeki et al.
	2003/0225047 A1	12/2003	Caubel et al.	2008/0026040 A1	1/2008	Farr et al.
	2003/0225048 A1	12/2003	Caubel et al.	2008/0038219 A1	2/2008	Mosbaugh et al.
	2003/0235596 A1	12/2003	Gao et al.	2008/0039405 A1	2/2008	Langley et al.
	2003/0236236 A1	12/2003	Chen et al.	2008/0050317 A1	2/2008	Tamarkin et al.
	2004/0022820 A1	2/2004	Anderson	2008/0051351 A1	2/2008	Ghisalberti
	2004/0039356 A1	2/2004	Maki et al.	2008/0063607 A1	3/2008	Tamarkin et al.
	2004/0043043 A1	3/2004	Schlyter et al.	2008/0069779 A1	3/2008	Tamarkin et al.
	2004/0048900 A1	3/2004	Flood	2008/0069791 A1	3/2008	Beissert
	2004/0087564 A1	5/2004	Wright et al.	2008/0095831 A1	4/2008	McGraw
	2004/0092494 A9	5/2004	Dudley	2008/0138390 A1	6/2008	Hsu et al.
	2004/0110732 A1	6/2004	Masini Eteve et al.	2008/0139392 A1	6/2008	Acosta Zara et al.
	2004/0138103 A1	7/2004	Patt	2008/0153789 A1	6/2008	Dmowski et al.
	2004/0146539 A1	7/2004	Gupta	2008/0175905 A1	7/2008	Liu et al.
	2004/0161435 A1	8/2004	Gupta	2008/0175908 A1	7/2008	Liu et al.
	2004/0191207 A1	9/2004	Lipari et al.	2008/0206156 A1	8/2008	Cronk
	2004/0210280 A1	10/2004	Liedtke	2008/0206159 A1	8/2008	Tamarkin et al.
	2004/0219124 A1	11/2004	Gupta	2008/0214512 A1	9/2008	Seitz et al.
	2004/0225140 A1	11/2004	Fernandez et al.	2008/0226698 A1	9/2008	Tang et al.
	2004/0241219 A1	12/2004	Hille et al.	2008/0227763 A1	9/2008	Lanquetin et al.
	2005/0003003 A1	1/2005	Basu et al.	2008/0234240 A1	9/2008	Duesterberg et al.
	2005/0014729 A1	1/2005	Pulaski	2008/0261931 A1	10/2008	Hedner et al.
	2005/0020550 A1	1/2005	Morris et al.	2009/0004246 A1	1/2009	Woolfson et al.
	2005/0054991 A1	3/2005	Tobyn et al.	2009/0010968 A1	1/2009	Allart et al.
	2005/0118244 A1	6/2005	Theobald et al.	2009/0011041 A1	1/2009	Musaeva et al.
	2005/0129756 A1	6/2005	Podhaisky et al.	2009/0017120 A1	1/2009	Trimble et al.
	2005/0152956 A1	7/2005	Dudley	2009/0022683 A1	1/2009	Song et al.
	2005/0186141 A1	8/2005	Gonda et al.	2009/0047357 A1	2/2009	Tomohira et al.
	2005/0196434 A1	9/2005	Brierre	2009/0060997 A1	3/2009	Seitz et al.
	2005/0220900 A1	10/2005	Popp et al.	2009/0081206 A1	3/2009	Leibovitz
				2009/0093440 A1	4/2009	Murad
				2009/0098069 A1	4/2009	Vacca
				2009/0099149 A1	4/2009	Liu et al.
				2009/0130029 A1	5/2009	Tamarkin et al.

## US 9,114,145 B2

Page 4

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2009/0175799	A1	7/2009	Tamarkin et al.	2012/0142645	A1	6/2012	Marx
2009/0186081	A1	7/2009	Holm et al.	2012/0148670	A1	6/2012	Kim et al.
2009/0197843	A1	8/2009	Notelovitz et al.	2012/0172343	A1	7/2012	Lindenthal et al.
2009/0203658	A1	8/2009	Marx et al.	2012/0184515	A1	7/2012	Klar et al.
2009/0227550	A1	9/2009	Mattern	2012/0231052	A1	9/2012	Sitruk Ware et al.
2009/0285869	A1	11/2009	Trimble	2012/0232011	A1	9/2012	Kneissel et al.
2009/0324714	A1	12/2009	Liu et al.	2012/0232042	A1	9/2012	Klar et al.
2010/0008985	A1	1/2010	Pellikaan et al.	2012/0263679	A1	10/2012	Marlow et al.
2010/0034838	A1	2/2010	Staniforth et al.	2012/0277249	A1	11/2012	Andersson et al.
2010/0034880	A1	2/2010	Sintov et al.	2012/0277727	A1	11/2012	Doshi et al.
2010/0055138	A1	3/2010	Margulies et al.	2012/0295911	A1	11/2012	Mannion et al.
2010/0086501	A1	4/2010	Chang et al.	2012/0301517	A1	11/2012	Zhang et al.
2010/0119585	A1	5/2010	Hille et al.	2012/0301538	A1	11/2012	Gordon Beresford et al.
2010/0143420	A1	6/2010	Shenoy et al.	2012/0302535	A1	11/2012	Caufriez et al.
2010/0143481	A1	6/2010	Shenoy et al.	2012/0316130	A1	12/2012	Hendrix
2010/0150993	A1	6/2010	Theobald et al.	2012/0316496	A1	12/2012	Hoffmann et al.
2010/0204326	A1	8/2010	D Souza	2012/0321579	A1	12/2012	Edelson et al.
2010/0210994	A1	8/2010	Zarif	2012/0322779	A9	12/2012	Voskuhl
2010/0221195	A1	9/2010	Tamarkin et al.	2012/0328549	A1	12/2012	Edelson et al.
2010/0227797	A1	9/2010	Axelsson et al.	2012/0329738	A1	12/2012	Liu
2010/0247482	A1	9/2010	Cui et al.	2013/0004619	A1	1/2013	Chow et al.
2010/0247635	A1	9/2010	Rosenberg et al.	2013/0011342	A1	1/2013	Tamarkin et al.
2010/0273730	A1	10/2010	Hsu et al.	2013/0017239	A1	1/2013	Viladot Petit et al.
2010/0278759	A1	11/2010	Murad	2013/0023505	A1	1/2013	Garfield et al.
2010/0279988	A1	11/2010	Setiawan et al.	2013/0023823	A1	1/2013	Simpson et al.
2010/0291191	A1	11/2010	Shoichet et al.	2013/0028850	A1	1/2013	Tamarkin et al.
2010/0292199	A1	11/2010	Leverd et al.	2013/0029957	A1	1/2013	Giliyar et al.
2010/0322884	A1	12/2010	Dipietro et al.	2013/0045266	A1	2/2013	Choi et al.
2011/0039814	A1	2/2011	Huatan et al.	2013/0045953	A1	2/2013	Sitruk Ware et al.
2011/0087192	A1	4/2011	Uhland et al.	2013/0059795	A1	3/2013	Lo et al.
2011/0098258	A1	4/2011	Masini Eveve et al.	2013/0064897	A1	3/2013	Binay
2011/0104268	A1	5/2011	Pachot et al.	2013/0072466	A1	3/2013	Choi et al.
2011/0130372	A1	6/2011	Agostinacchio et al.	2013/0084257	A1	4/2013	Ishida et al.
2011/0142945	A1	6/2011	Chen et al.	2013/0085123	A1	4/2013	Li et al.
2011/0152840	A1	6/2011	Lee et al.	2013/0089574	A1	4/2013	Schmidt Gollwitzer et al.
2011/0158920	A1	6/2011	Morley et al.	2013/0090318	A1	4/2013	Ulmann et al.
2011/0171140	A1	7/2011	Illum et al.	2013/0102781	A1	4/2013	Bevill et al.
2011/0190201	A1	8/2011	Hyde et al.	2013/0108551	A1	5/2013	Langereis et al.
2011/0195031	A1	8/2011	Du	2013/0116215	A1	5/2013	Coma et al.
2011/0238003	A1	9/2011	Bruno Raimondi et al.	2013/0116222	A1	5/2013	Arnold et al.
2011/0244043	A1	10/2011	Xu et al.	2013/0122051	A1	5/2013	Abidi et al.
2011/0250256	A1	10/2011	Hyun Oh et al.	2013/0123175	A1	5/2013	Hill et al.
2011/0250259	A1	10/2011	Buckman	2013/0123220	A1	5/2013	Queiroz
2011/0262373	A1	10/2011	Umbert Millet	2013/0123351	A1	5/2013	Dewitt
2011/0275584	A1	11/2011	Wilckens et al.	2013/0131027	A1	5/2013	Pakkalin et al.
2011/0281832	A1	11/2011	Li et al.	2013/0131028	A1	5/2013	Snyder et al.
2011/0287094	A1	11/2011	Penhasi et al.	2013/0131029	A1	5/2013	Bakker et al.
2011/0294738	A1	12/2011	Ren et al.	2013/0149314	A1	6/2013	Bullerdiek et al.
2011/0300167	A1	12/2011	McMurry et al.	2013/0164225	A1	6/2013	Tamarkin et al.
2011/0301087	A1	12/2011	McBride et al.	2013/0164346	A1	6/2013	Lee et al.
2011/0306579	A1	12/2011	Stein	2013/0165744	A1	6/2013	Carson et al.
2011/0318405	A1	12/2011	Erwin	2013/0178452	A1	7/2013	King
2011/0318431	A1	12/2011	Gulati	2013/0183254	A1	7/2013	Zhou et al.
2012/0021041	A1	1/2012	Rossi et al.	2013/0183325	A1	7/2013	Bottoni et al.
2012/0028888	A1	2/2012	Janz et al.	2013/0189193	A1	7/2013	Tamarkin et al.
2012/0028910	A1	2/2012	Combal et al.	2013/0189196	A1	7/2013	Tamarkin et al.
2012/0028936	A1	2/2012	Gloger et al.	2013/0189230	A1	7/2013	Shoichet et al.
2012/0046264	A1	2/2012	Simes et al.	2013/0189368	A1	7/2013	Mosqueira et al.
2012/0046518	A1	2/2012	Yoakum et al.	2013/0210709	A1	8/2013	McMurry et al.
2012/0058171	A1	3/2012	De Graaff et al.	2013/0216550	A1	8/2013	Penninger et al.
2012/0058962	A1	3/2012	Cumming et al.	2013/0216596	A1	8/2013	Viladot Petit et al.
2012/0058979	A1	3/2012	Keith et al.	2013/0224177	A1	8/2013	Kim et al.
2012/0064135	A1	3/2012	Levin et al.	2013/0224257	A1	8/2013	Sah et al.
2012/0065179	A1	3/2012	Andersson	2013/0224268	A1	8/2013	Alam et al.
2012/0087872	A1	4/2012	Tamarkin et al.	2013/0224300	A1	8/2013	Maggio
2012/0101073	A1	4/2012	Mannion et al.	2013/0225412	A1	8/2013	Sardari Lodriche et al.
2012/0121517	A1	5/2012	Song et al.	2013/0225542	A1	8/2013	Poegh et al.
2012/0121692	A1	5/2012	Xu et al.	2013/0226113	A1	8/2013	Schumacher et al.
2012/0122829	A1	5/2012	Taravella et al.	2013/0243696	A1	9/2013	Wang et al.
2012/0128654	A1	5/2012	Terpstra et al.	2013/0245253	A1	9/2013	Marx et al.
2012/0128683	A1	5/2012	Shantha	2013/0245570	A1	9/2013	Jackson
2012/0128733	A1	5/2012	Perrin et al.	2013/0261096	A1	10/2013	Merian et al.
2012/0129773	A1	5/2012	Geier et al.	2013/0266645	A1	10/2013	Becker et al.
2012/0129819	A1	5/2012	Vancaillie et al.	2013/0267485	A1	10/2013	Da Silva Maia Filho
2012/0136013	A1	5/2012	Li et al.	2013/0273167	A1	10/2013	Lee et al.
				2013/0274211	A1	10/2013	Burman et al.
				2013/0280213	A1	10/2013	Voskuhl
				2013/0316374	A1	11/2013	Penninger et al.
				2013/0317065	A1	11/2013	Tatani et al.



## US 9,114,145 B2

Page 5

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2013/0317315	A1	11/2013	Lu et al.
2013/0324565	A1	12/2013	Li et al.
2013/0331363	A1	12/2013	Li et al.
2013/0338124	A1	12/2013	Li et al.
2013/0345187	A1	12/2013	Rodriguez Oquendo
2014/0018335	A1	1/2014	Tatani et al.
2014/0024590	A1	1/2014	Weidhaas et al.
2014/0031289	A1	1/2014	Song et al.
2014/0031323	A1	1/2014	Perez
2014/0066416	A1	3/2014	Leunis et al.
2014/0072531	A1	3/2014	Kim et al.
2014/0079686	A1	3/2014	Barman et al.
2014/0088058	A1	3/2014	Maurizio
2014/0088059	A1	3/2014	Perumal et al.
2014/0094426	A1	4/2014	Drummond et al.
2014/0100159	A1	4/2014	Conrad
2014/0100206	A1	4/2014	Bernick et al.
2014/0113889	A1	4/2014	Connor et al.
2014/0127185	A1	5/2014	Stein et al.
2014/0127280	A1	5/2014	Duesterberg et al.
2014/0127308	A1	5/2014	Opara et al.
2014/0128798	A1	5/2014	Janson et al.
2014/0148491	A1	5/2014	Valia et al.
2014/0186332	A1	7/2014	Ezrin et al.
2014/0187487	A1	7/2014	Shoichet et al.
2014/0193523	A1	7/2014	Henry
2014/0194396	A1	7/2014	Li et al.
2014/0206616	A1	7/2014	Ko et al.

## FOREIGN PATENT DOCUMENTS

WO	WO2012098090	A1	7/2012
WO	WO2012116277	A1	8/2012
WO	WO2012118563	A2	9/2012
WO	WO2012120365	A1	9/2012
WO	WO2012127501	A2	9/2012
WO	WO2012156561	A1	11/2012
WO	WO2012156822	A1	11/2012
WO	WO2012158483	A2	11/2012
WO	WO2012166909	A1	12/2012
WO	WO2012170578	A1	12/2012
WO	WO2013011501	A1	1/2013
WO	WO2013025449	A1	2/2013
WO	WO2013028639	A1	2/2013
WO	WO2013035101	A1	3/2013
WO	WO2013044067	A1	3/2013
WO	WO2013045404	A2	4/2013
WO	WO2013059285	A1	4/2013
WO	WO2013063279	A1	5/2013
WO	WO2013064620	A1	5/2013
WO	WO2013071281	A1	5/2013
WO	WO2013088254		6/2013
WO	WO2013102665	A1	7/2013
WO	WO2013106437	A1	7/2013
WO	WO2013113690		8/2013
WO	WO2013124415	A1	8/2013
WO	WO2013127727	A1	9/2013
WO	WO2013127728	A1	9/2013

WO	WO2013144356	A1	10/2013
WO	WO2013149258	A2	10/2013
WO	WO2013158424	A2	10/2013
WO	WO2013158454	A2	10/2013
WO	WO2013170052	A1	11/2013
WO	WO2013178587	A1	12/2013
WO	WO2013181449	A1	12/2013
WO	WO2014001904	A1	1/2014
WO	WO2014004424	A1	1/2014
WO	WO2014009434	A1	1/2014
WO	WO2014018569	A1	1/2014
WO	WO2014018570	A1	1/2014
WO	WO2014018571	A2	1/2014
WO	WO2014018856	A1	1/2014
WO	WO2014018932	A2	1/2014
WO	WO2014031958	A1	2/2014
WO	WO2014041120	A1	3/2014
WO	WO2014052792	A1	4/2014
WO	WO2014056897	A1	4/2014
WO	WO2014066442	A2	5/2014
WO	WO2014074846	A1	5/2014
WO	WO2014076231	A1	5/2014
WO	WO2014076569	A2	5/2014
WO	WO2014081598	A1	5/2014
WO	WO2014086739	A1	6/2014
WO	WO2014093114	A1	6/2014
WO	WO2014104784	A1	7/2014

## OTHER PUBLICATIONS

Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.

Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.

Gattefossé Sas, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.

Gattefossé Sas, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.

Gattefossé Sas, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.

Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," Clinical Pharmacy, 1990, vol. 9, No. 5, pp. 366-371.

Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," Journal of Pharmaceutical Sciences, vol. 86, No. 1, Jan. 1997, pp. 13-18.

Sasol Olefins & Surfactants GmbH, Excipients for Pharmaceuticals, 2010, 28 pages.

Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," Food and Chemical Toxicology, 72 (2014) pp. 40-50.

Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," Journal of Pharmaceutical Sciences, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.

ZRT Laboratory, Provider Data Sheet, About Dried Blood Spot Testing, 2014, 3 pages.

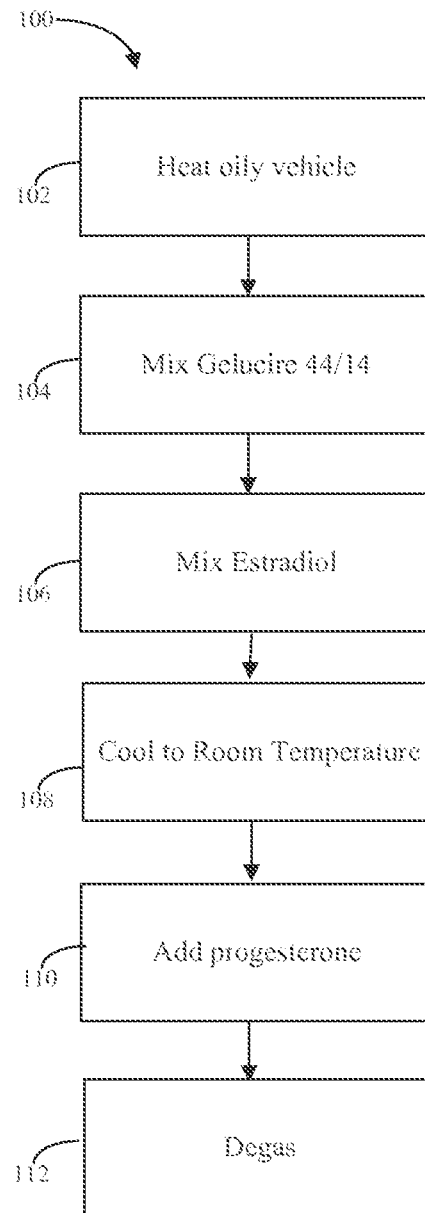
\* cited by examiner

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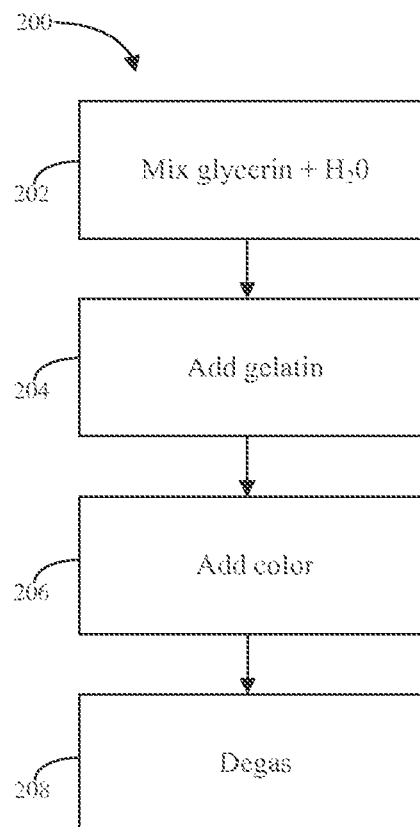
**Aug. 25, 2015**

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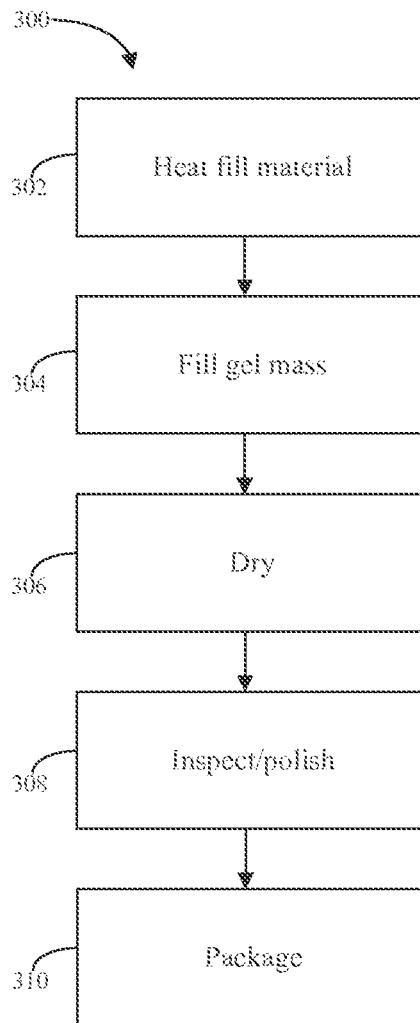
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**Fig. 1**



**Fig. 2**



**Fig. 3**

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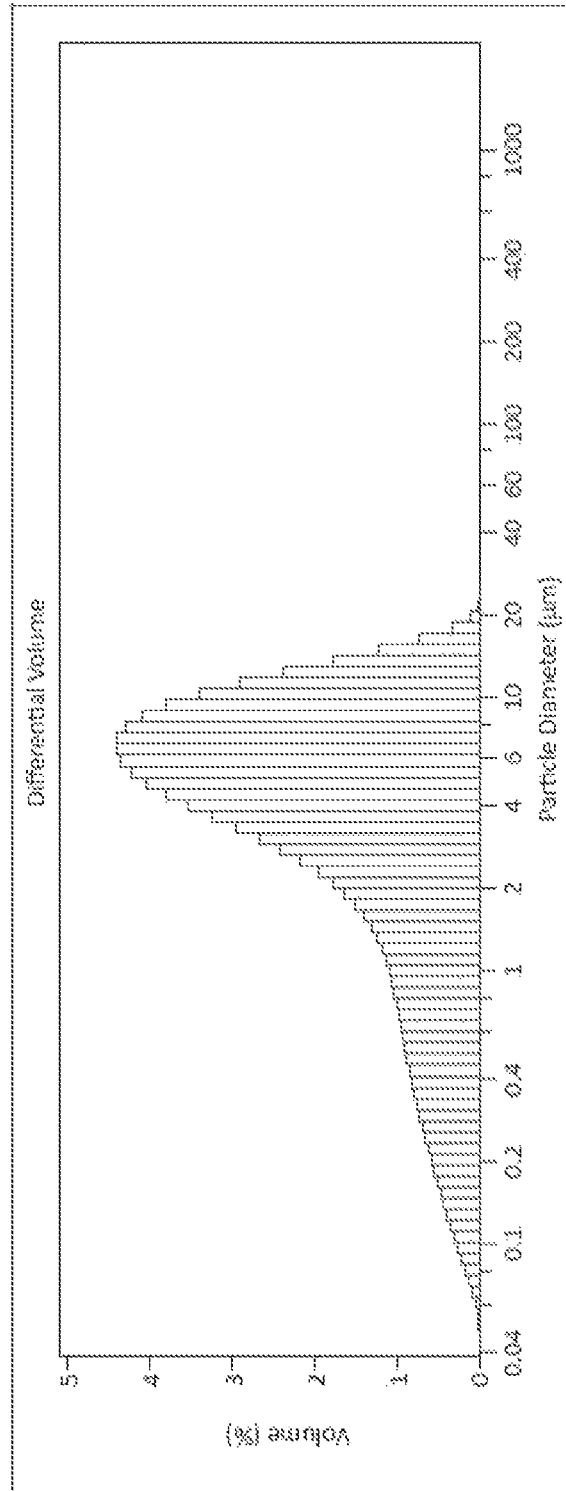


FIG. 4

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# **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

## **CROSS-REFERENCES TO RELATED APPLICATIONS**

This application is a continuation of U.S. patent application Ser. No. 14/099,545, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Dec. 6, 2013, which application is a divisional of U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which application claims priority to the following U.S. Provisional Patent Applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

## **FIELD OF THE INVENTION**

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

## **BACKGROUND OF THE INVENTION**

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a

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constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

5 Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

10 "Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

15 These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

20 Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

## **SUMMARY OF THE INVENTION**

35 According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

## **BRIEF DESCRIPTION OF THE DRAWINGS**

40 The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

60 FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

65 FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.



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## DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

## A. DEFINITIONS

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC,  $C_{max}$ , and optionally,  $T_{max}$ .

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “ $C_{max}$ ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “ $T_{max}$ ” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC,  $C_{max}$  and, optionally,  $T_{max}$  are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

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The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

## B. DESCRIPTION AND PREFERRED EMBODIMENTS

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to

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about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 $\beta$ -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from

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about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017  $\mu$ m to 2000  $\mu$ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4  $\mu$ m to 2000  $\mu$ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

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Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol: Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Miglyol and Capmul PG 8 and/or PG 10; Campul MCM; Capmul MCM and a non-ionic surfactant; and Campul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Campul MCM and Gelucire can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

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In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

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In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

## EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

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## Example 1

## Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

\*Literature reference - Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

## Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

## Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold



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cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol:Miglyol:Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

## Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

## Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

## Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

## Example 7

## Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

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As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

## Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

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For example, Campul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/-2° C. Gelucire 44/14 may be added to the Campul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Campul MCM.

Heat may be removed from the Gelucire 44/14 and Campul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Campul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

## Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is



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removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxy-1-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279  $\mu\text{m}$ , an X75 of 7.442  $\mu\text{m}$ , and an X25 of 1.590  $\mu\text{m}$ . The Beckman Device also yielded that the mean particle size is 4.975  $\mu\text{m}$ , the median particle size is 4.279  $\mu\text{m}$ , the mode particle size is 6.453  $\mu\text{m}$ , and the standard deviation is 3.956  $\mu\text{m}$ . A graph of the particle distribution obtained is shown in FIG. 4.

## Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0  $\mu\text{m}$ , an X75 of 17.3  $\mu\text{m}$ , and an X25 of 5.3  $\mu\text{m}$ . The Beckman Device also yielded that the mean particle size is 11.8  $\mu\text{m}$ , the median particle size is 11.04  $\mu\text{m}$ , the mode particle size is 13.6  $\mu\text{m}$ , and the standard deviation is 7.8  $\mu\text{m}$ .

## Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

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TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	INGRE-DIENT(S)	Label Claim (mg)	% w/w	Qty/Cap-sule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemi-hydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

## Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:			100.000	200.00 mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemi-hydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until

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dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

#### Example 16

Progesterone and Estradiol Combination Study Under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla.) and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condi-

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tion, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ± 20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

#### Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ± 5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

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With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+/-3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/-10° C. The wedge temperature may be 38° C.+/-3° C. The drum cooling temperature may be 4° C.+/-2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight ±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A method of treating a menopause-related symptom in a woman comprising: administering to the woman an effective amount of a pharmaceutical composition, the pharmaceutical composition comprising:

solubilized estradiol;  
suspended progesterone; and  
a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;

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wherein at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises an effective amount at least one of mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid.

2. The method of claim 1, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

3. The method of claim 1, wherein the formulation is formulated as a gelatin capsule.

4. The method of claim 1, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

5. The method of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

6. The method of claim 1, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and a 2 mg estradiol tablet.

7. A method of treating a menopause symptom in a woman comprising: administering a pharmaceutical composition to the woman, the pharmaceutical composition comprising:

solubilized estradiol;  
suspended progesterone; and

a solubilizing agent, the solubilizing agent comprising an effective amount mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid;

wherein the estradiol and the suspended progesterone are present in the solubilizing agent, the estradiol and progesterone are uniformly dispersed, and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the estradiol does not precipitate for at least 14 days.

8. The method of claim 7, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

9. The method of claim 7, wherein the formulation is formulated as a gelatin capsule.

10. The method of claim 7, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

11. The method of claim 7, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

12. The method of claim 7, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and a 2 mg estradiol tablet.

13. A method of treating a menopause symptom comprising: administering an effective amount of a pharmaceutical composition to a woman, the pharmaceutical composition comprising:

solubilized estradiol;  
suspended progesterone; and

a solubilizing agent, the estradiol being stable in the solubilizing agent for at least 14 days;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent;

wherein the estradiol and progesterone are uniformly dispersed;

wherein at least about 90% of the estradiol is solubilized in the solubilizing agent, and

wherein the solubilizing agent comprises an effective amount mono-, di-, and triglycerides containing an ester of a C6-C12 fatty acid.

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14. The method of claim 13, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

15. The method of claim 13, wherein the formulation is formulated as a gelatin capsule. 5

16. The method of claim 13, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

17. The method of claim 13, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1. 10

18. The method of claim 13, wherein the composition is bioequivalent to a 200 mg progesterone soft gel capsule and a 2 mg estradiol tablet.

\* \* \* \* \*

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UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 9,114,145 B2  
APPLICATION NO. : 14/475946  
DATED : August 25, 2015  
INVENTOR(S) : Brian A. Bernick et al.

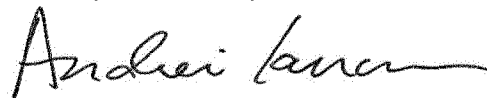
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this  
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu  
*Director of the United States Patent and Trademark Office*

# EXHIBIT I





US009114146B2

(12) **United States Patent**  
**Bernick et al.**

(10) **Patent No.: US 9,114,146 B2**  
(45) **Date of Patent: \*Aug. 25, 2015**

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

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(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/476,040**

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(65) **Prior Publication Data**

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#### Related U.S. Application Data

(60) Continuation of application No. 14/099,545, filed on Dec. 6, 2013, now Pat. No. 8,846,648, which is a division of application No. 13/684,002, filed on Nov. 21, 2012, now Pat. No. 8,633,178.

(60) Provisional application No. 61/662,265, filed on Jun. 20, 2012, provisional application No. 61/661,302, filed on Jun. 18, 2012, provisional application No. 61/563,408, filed on Nov. 23, 2011.

(51) **Int. Cl.**

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**A61K 9/16** (2006.01)

**A61K 31/565** (2006.01)

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(52) **U.S. Cl.**

CPC . **A61K 31/57** (2013.01); **A61K 9/16** (2013.01); **A61K 9/4858** (2013.01); **A61K 9/7023** (2013.01); **A61K 31/565** (2013.01)

(58) **Field of Classification Search**

USPC ..... 514/169; 424/452  
See application file for complete search history.

(56) **References Cited**

#### U.S. PATENT DOCUMENTS

2,232,438 A 2/1941 Butenandt  
5,538,736 A 7/1996 Hoffmann et al.  
5,556,635 A 9/1996 Istin et al.  
5,580,572 A 12/1996 Mikler et al.

5,605,702 A 2/1997 Teillaud et al.  
5,607,691 A 3/1997 Hale et al.  
5,607,693 A 3/1997 Bonte et al.  
5,609,617 A 3/1997 Shealy et al.  
5,626,866 A 5/1997 Ebert et al.  
5,653,983 A 8/1997 Meybeck et al.  
5,660,839 A 8/1997 Allec et al.  
5,662,927 A 9/1997 Ehrlich et al.  
5,663,160 A 9/1997 Meybeck et al.  
5,686,097 A 11/1997 Taskovich et al.  
5,693,335 A 12/1997 Xia et al.  
5,700,480 A 12/1997 Hille et al.  
5,719,197 A 2/1998 Kanios et al.  
5,770,220 A 6/1998 Meconi et al.  
5,770,227 A 6/1998 Dong et al.  
5,780,044 A 7/1998 Yewey et al.  
5,780,050 A 7/1998 Jain et al.  
5,788,984 A 8/1998 Guenther et al.  
5,820,878 A 10/1998 Hirano et al.  
5,840,327 A 11/1998 Gale et al.  
5,843,468 A 12/1998 Burkoth et al.  
5,843,979 A 12/1998 Wille et al.  
5,858,394 A 1/1999 Lipp et al.  
5,863,552 A 1/1999 Yue  
5,882,676 A 3/1999 Lee et al.  
5,885,612 A 3/1999 Meconi et al.  
5,888,533 A 3/1999 Dunn  
5,891,462 A 4/1999 Carrara

(Continued)

#### FOREIGN PATENT DOCUMENTS

WO WO9619975 7/1996  
WO WO0241878 5/2002

(Continued)

#### OTHER PUBLICATIONS

Abitec Corporation, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.

Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," Southern Medical Journal, vol. 107, No. 7, Jul. 2014, pp. 433-436.

Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.

Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.

(Continued)

Primary Examiner — Dennis J Parad

(74) Attorney, Agent, or Firm — Kilpatrick Townsend & Stockton; Marlan D. Walker

(57) **ABSTRACT**

Estrogen and progesterone replacement therapies are provided herein. Among others, the following formulations are provided herein: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone.

**15 Claims, 4 Drawing Sheets**

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

5,902,603	A	5/1999	Chen et al.	7,153,522	B1	12/2006	Ikeura et al.
5,904,931	A	5/1999	Lipp et al.	7,175,850	B2	2/2007	Cevc
5,906,830	A	5/1999	Farinas et al.	7,198,800	B1	4/2007	Ko
5,912,010	A	6/1999	Wille et al.	7,381,427	B2	6/2008	Ancira et al.
5,919,477	A	7/1999	Bevan et al.	7,456,159	B2	11/2008	Houze et al.
5,942,243	A	8/1999	Shah	7,498,303	B2	3/2009	Arnold et al.
5,942,531	A	8/1999	Diaz et al.	7,534,780	B2	5/2009	Wyrwa et al.
5,952,000	A	9/1999	Venkateshwaran et al.	7,569,274	B2	8/2009	Besse et al.
5,968,919	A	10/1999	Samour et al.	7,799,769	B2	9/2010	White et al.
5,985,311	A	11/1999	Cordes et al.	7,815,936	B2	10/2010	Hasenzahl et al.
5,985,850	A	11/1999	Falk et al.	7,829,116	B2	11/2010	Griswold et al.
5,989,568	A	11/1999	Breton et al.	7,850,992	B2	12/2010	Kim et al.
6,007,835	A	12/1999	Bon Lapillonne et al.	7,854,753	B2	12/2010	Kraft et al.
6,010,715	A	1/2000	Wick et al.	7,871,643	B2	1/2011	Lizio et al.
6,013,276	A	1/2000	Math et al.	7,925,519	B2	4/2011	Greene
6,024,974	A	2/2000	Li	7,945,459	B2	5/2011	Grace et al.
6,030,948	A	2/2000	Mann	7,960,368	B2	6/2011	Nickisch et al.
6,040,340	A	3/2000	Chwalisz et al.	8,048,017	B2	11/2011	Xu
6,068,853	A	5/2000	Giannos et al.	8,063,030	B2	11/2011	Ellman
6,087,352	A	7/2000	Trout	8,071,576	B2	12/2011	Coelingh Bennink et al.
6,090,404	A	7/2000	Meconi et al.	8,075,916	B2	12/2011	Song et al.
6,106,848	A	8/2000	Preuilh et al.	8,075,917	B2	12/2011	Chung et al.
6,124,362	A	9/2000	Bradbury et al.	8,076,317	B2	12/2011	Kulmann
6,139,868	A	10/2000	Hoffmann	8,080,553	B2	12/2011	Keith et al.
6,149,935	A	11/2000	Chiang et al.	8,096,940	B2	1/2012	Josephson et al.
6,187,323	B1	2/2001	Aiache et al.	8,114,152	B2	2/2012	Furst
6,217,886	B1	4/2001	Onyueksel et al.	8,114,442	B2	2/2012	Tucker et al.
6,225,297	B1	5/2001	Stockemann et al.	8,119,741	B2	2/2012	Pavlin
6,228,383	B1	5/2001	Hansen et al.	8,121,886	B2	2/2012	Azar
6,228,852	B1	5/2001	Shaak	8,124,118	B2	2/2012	Lennernaes et al.
6,242,509	B1	6/2001	Berger et al.	8,124,595	B2	2/2012	Boissonneault
6,245,811	B1	6/2001	Horrobin et al.	8,147,561	B2	4/2012	Binmoeller
6,267,984	B1	7/2001	Beste et al.	8,148,546	B2	4/2012	Schuster et al.
6,274,165	B1	8/2001	Meconi et al.	8,158,613	B2	4/2012	Staniforth et al.
6,303,132	B1	10/2001	Nelson	8,163,722	B2	4/2012	Savoir et al.
6,303,588	B1	10/2001	Danielov	8,177,449	B2	5/2012	Bayly et al.
6,312,703	B1	11/2001	Orthofer	8,187,615	B2	5/2012	Friedman
6,328,987	B1	12/2001	Marini	8,195,403	B2	6/2012	Ishikawa et al.
6,344,211	B1	2/2002	Hille	8,221,785	B2	7/2012	Chien
6,372,245	B1	4/2002	Bowman et al.	8,222,237	B2	7/2012	Nickisch et al.
6,420,352	B1	7/2002	Knowles	8,257,724	B2	9/2012	Cromack et al.
6,432,438	B1	8/2002	Shukla	8,257,725	B2	9/2012	Cromack et al.
6,451,300	B1	9/2002	Dunlop et al.	8,268,352	B2	9/2012	Vaya et al.
6,465,004	B1	10/2002	Rossi Montero et al.	8,268,806	B2	9/2012	Labrie
6,465,005	B1	10/2002	Biali et al.	8,268,878	B2	9/2012	Armer et al.
6,465,006	B1	10/2002	Zhang et al.	8,288,366	B2	10/2012	Chochinov et al.
6,495,160	B2	12/2002	Esposito et al.	8,318,898	B2	11/2012	Fasel et al.
6,521,250	B2	2/2003	Meconi et al.	8,324,193	B2	12/2012	Lee Sepsick et al.
6,531,149	B1	3/2003	Kirstgen et al.	8,337,814	B2	12/2012	Osbakken et al.
6,538,039	B2	3/2003	Laurent	8,344,007	B2	1/2013	Tang et al.
6,548,053	B1	4/2003	Stewart et al.	8,353,863	B2	1/2013	Imran
6,555,131	B1	4/2003	Wolff et al.	8,357,723	B2	1/2013	Satyam
6,562,367	B1	5/2003	Wolff et al.	8,361,995	B2	1/2013	Schramm
6,562,370	B2	5/2003	Luo et al.	8,362,091	B2	1/2013	Tamarkin et al.
6,562,790	B2	5/2003	Chein	8,372,424	B2	2/2013	Berry et al.
6,599,519	B1	7/2003	Seo et al.	8,372,806	B2	2/2013	Boehler et al.
6,610,674	B1	8/2003	Schreiber	8,377,482	B2	2/2013	Laurie et al.
6,635,274	B1	10/2003	Masiz et al.	8,377,994	B2	2/2013	Gray et al.
6,638,528	B1	10/2003	Kanios	8,394,759	B2	3/2013	Barathur et al.
6,649,155	B1	11/2003	Dunlop et al.	8,415,332	B2	4/2013	Diliberti et al.
6,682,757	B1	1/2004	Wright	8,435,972	B2	5/2013	Stein et al.
6,708,822	B1	3/2004	Muni	8,449,879	B2	5/2013	Laurent Applegate et al.
6,720,001	B2	4/2004	Chen et al.	8,450,108	B2	5/2013	Boyce
6,743,448	B2	6/2004	Kryger	8,454,945	B2	6/2013	Mccook et al.
6,750,291	B2	6/2004	Kim et al.	8,455,468	B2	6/2013	Hoffman et al.
6,821,524	B2	11/2004	Marini	8,461,138	B2	6/2013	Boissonneault
6,911,211	B2	6/2005	Eini et al.	8,476,252	B2	7/2013	Achleitner et al.
6,960,337	B2	11/2005	Daniels et al.	8,481,488	B2	7/2013	Carter
6,974,569	B2	12/2005	Dunlop et al.	8,486,374	B2	7/2013	Tamarkin et al.
6,995,149	B1	2/2006	Endrikat et al.	8,486,442	B2	7/2013	Matsushita et al.
7,004,321	B1	2/2006	Palm et al.	8,492,368	B2	7/2013	Vanlandingham et al.
7,030,104	B2	4/2006	Gray et al.	8,507,467	B2	8/2013	Matsui et al.
7,094,228	B2	8/2006	Zhang et al.	8,512,693	B2	8/2013	Capito et al.
7,097,853	B1	8/2006	Garbe et al.	8,512,754	B2	8/2013	Needham
7,105,573	B2	9/2006	Krajcik et al.	8,518,376	B2	8/2013	Tamarkin et al.
				8,536,159	B2	9/2013	Li et al.
				8,540,967	B2	9/2013	Barrett et al.
				8,541,400	B2	9/2013	Johnsson et al.
				8,551,462	B2	10/2013	Goldstein et al.

## US 9,114,146 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

8,557,281	B2	10/2013	Halliday et al.	2004/0161435	A1	8/2004	Gupta
8,568,374	B2	10/2013	De Graaff et al.	2004/0191207	A1	9/2004	Lipari et al.
8,591,951	B2	11/2013	Kohn et al.	2004/0210280	A1	10/2004	Liedtke
8,613,951	B2	12/2013	Zale et al.	2004/0219124	A1	11/2004	Gupta
8,633,178	B2	1/2014	Bernick et al.	2004/0225140	A1	11/2004	Fernandez et al.
8,633,180	B2	1/2014	Li et al.	2004/0241219	A1	12/2004	Hille et al.
8,636,787	B2	1/2014	Sabaria	2004/0243437	A1	12/2004	Grace et al.
8,636,982	B2	1/2014	Tamarkin et al.	2005/0003003	A1	1/2005	Basu et al.
8,653,129	B2	2/2014	Fein et al.	2005/0014729	A1	1/2005	Pulaski
8,658,627	B2	2/2014	Voskuhl	2005/0020550	A1	1/2005	Morris et al.
8,663,692	B1	3/2014	Mueller et al.	2005/0054991	A1	3/2005	Tobyn et al.
8,663,703	B2	3/2014	Lerner et al.	2005/0118244	A1	6/2005	Theobald et al.
8,664,207	B2	3/2014	Li et al.	2005/0129756	A1	6/2005	Podhaisky et al.
8,669,293	B2	3/2014	Levy et al.	2005/0152956	A1	7/2005	Dudley
8,679,552	B2	3/2014	Guthery	2005/0186141	A1	8/2005	Gonda et al.
8,694,358	B2	4/2014	Tryfon	2005/0196434	A1	9/2005	Brierre
8,697,127	B2	4/2014	Sah	2005/0220900	A1	10/2005	Popp et al.
8,697,710	B2	4/2014	Li et al.	2005/0228692	A1	10/2005	Hodgdon
8,703,105	B2	4/2014	Tamarkin et al.	2005/0228718	A1	10/2005	Austin
8,709,385	B2	4/2014	Tamarkin et al.	2005/0239747	A1	10/2005	Yang et al.
8,709,451	B2	4/2014	Nam et al.	2005/0239758	A1	10/2005	Roby
8,715,735	B2	5/2014	Funke et al.	2005/0244360	A1	11/2005	Billoni
8,721,331	B2	5/2014	Raghuprasad	2005/0266088	A1	12/2005	Hinrichs et al.
8,722,021	B2	5/2014	Friedman et al.	2005/0271597	A1	12/2005	Keith
8,734,846	B2	5/2014	Ali et al.	2005/0272685	A1	12/2005	Hung
8,735,381	B2	5/2014	Podolski	2006/0009428	A1	1/2006	Grubb et al.
8,741,336	B2	6/2014	Dipierro et al.	2006/0034904	A1	2/2006	Weimann
8,741,373	B2	6/2014	Bromley et al.	2006/0040904	A1	2/2006	Ahmed et al.
8,753,661	B2	6/2014	Steinmueller Nethl et al.	2006/0078618	A1	4/2006	Constantinides et al.
8,784,882	B2	7/2014	Mattern	2006/0084704	A1	4/2006	Shih et al.
8,846,648	B2	9/2014	Bernick et al.	2006/0088580	A1	4/2006	Meconi et al.
8,846,649	B2	9/2014	Bernick et al.	2006/0100180	A1	5/2006	Nubbemeyer et al.
8,933,059	B2	1/2015	Bernick et al.	2006/0121102	A1	6/2006	Chiang
8,987,237	B2	3/2015	Bernick et al.	2006/0165744	A1	7/2006	Jamil et al.
8,987,238	B2	3/2015	Bernick et al.	2006/0193789	A1	8/2006	Tamarkin et al.
8,993,548	B2	3/2015	Bernick et al.	2006/0233743	A1	10/2006	Kelly
8,993,549	B2	3/2015	Bernick et al.	2006/0233841	A1	10/2006	Brodbeck et al.
9,006,222	B2	4/2015	Bernick et al.	2006/0246122	A1	11/2006	Langguth et al.
9,012,434	B2	4/2015	Bernick et al.	2006/0247221	A1	11/2006	Coelingh Bennink et al.
2001/0009673	A1	7/2001	Lipp et al.	2006/0251581	A1	11/2006	McIntyre et al.
2001/0023261	A1	9/2001	Ryoo et al.	2006/0275218	A1	12/2006	Tamarkin et al.
2001/0032125	A1	10/2001	Bhan et al.	2006/0276414	A1	12/2006	Coelingh Bennink et al.
2001/0053383	A1	12/2001	Miranda et al.	2006/0292223	A1	12/2006	Woolfson et al.
2002/0035070	A1	3/2002	Gardlik et al.	2007/0009559	A1	1/2007	Li et al.
2002/0119174	A1	8/2002	Gardlik et al.	2007/0009594	A1	1/2007	Grubb et al.
2002/0119198	A1	8/2002	Gao et al.	2007/0010550	A1	1/2007	McKenzie
2002/0142017	A1	10/2002	Simonnet	2007/0014839	A1	1/2007	Bracht
2002/0169205	A1	11/2002	Chwalisz et al.	2007/0015698	A1	1/2007	Kleinman et al.
2002/0193758	A1	12/2002	Sandberg	2007/0037780	A1	2/2007	Ebert et al.
2002/0197286	A1	12/2002	Brandman et al.	2007/0037782	A1	2/2007	Hibino et al.
2003/0003139	A1	1/2003	Lipp et al.	2007/0078091	A1	4/2007	Hubler et al.
2003/0027772	A1	2/2003	Breton	2007/0128263	A1	6/2007	Gargiulo et al.
2003/0044453	A1	3/2003	Dittgen et al.	2007/0154533	A1	7/2007	Dudley
2003/0077297	A1*	4/2003	Chen et al. .... 424/400	2007/0167418	A1	7/2007	Ferguson
2003/0091620	A1	5/2003	Fikstad et al.	2007/0185068	A1	8/2007	Ferguson et al.
2003/0109507	A1	6/2003	Franke et al.	2007/0190022	A1	8/2007	Bacopoulos et al.
2003/0113268	A1	6/2003	Buenafae et al.	2007/0196415	A1	8/2007	Chen et al.
2003/0170295	A1	9/2003	Kim et al.	2007/0232574	A1	10/2007	Galey et al.
2003/0175329	A1	9/2003	Azarnoff et al.	2007/0248658	A1	10/2007	Zurdo Schroeder et al.
2003/0175333	A1	9/2003	Shefer et al.	2007/0254858	A1	11/2007	Cronk
2003/0219402	A1	11/2003	Rutter	2007/0255197	A1	11/2007	Humberstone et al.
2003/0225047	A1	12/2003	Caubel et al.	2007/0287688	A1	12/2007	Chan et al.
2003/0225048	A1	12/2003	Caubel et al.	2007/0292359	A1	12/2007	Friedman et al.
2003/0235596	A1	12/2003	Gao et al.	2007/0292461	A1	12/2007	Tamarkin et al.
2003/0236236	A1	12/2003	Chen et al.	2007/0292493	A1	12/2007	Brierre
2004/0022820	A1	2/2004	Anderson	2007/0298089	A1	12/2007	Saeki et al.
2004/0039356	A1	2/2004	Maki et al.	2008/0026040	A1	1/2008	Farr et al.
2004/0043043	A1	3/2004	Schlyter et al.	2008/0038219	A1	2/2008	Mosbaugh et al.
2004/0048900	A1	3/2004	Flood	2008/0039405	A1	2/2008	Langley et al.
2004/0087564	A1	5/2004	Wright et al.	2008/0050317	A1	2/2008	Tamarkin et al.
2004/0092494	A9	5/2004	Dudley	2008/0051351	A1	2/2008	Ghisalberti
2004/0093261	A1	5/2004	Jain et al.	2008/0063607	A1	3/2008	Tamarkin et al.
2004/0110732	A1	6/2004	Masini Eveve et al.	2008/0069779	A1	3/2008	Tamarkin et al.
2004/0138103	A1	7/2004	Patt	2008/0069791	A1	3/2008	Beissert
2004/0146539	A1	7/2004	Gupta	2008/0095831	A1	4/2008	McGraw
				2008/0138390	A1	6/2008	Hsu et al.
				2008/0139392	A1	6/2008	Acosta Zara et al.
				2008/0153789	A1	6/2008	Dmowski et al.
				2008/0175905	A1	7/2008	Liu et al.

## US 9,114,146 B2

Page 4

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2008/0175908	A1	7/2008	Liu et al.	2012/0021041	A1	1/2012	Rossi et al.
2008/0206156	A1	8/2008	Cronk	2012/0028888	A1	2/2012	Janz et al.
2008/0206159	A1	8/2008	Tamarkin et al.	2012/0028910	A1	2/2012	Combal et al.
2008/0214512	A1	9/2008	Seitz et al.	2012/0028936	A1	2/2012	Gloger et al.
2008/0226698	A1	9/2008	Tang et al.	2012/0046264	A1	2/2012	Simes et al.
2008/0227763	A1	9/2008	Lanquetin et al.	2012/0046518	A1	2/2012	Yoakum et al.
2008/0234240	A1	9/2008	Duesterberg et al.	2012/0058171	A1	3/2012	De Graaff et al.
2008/0261931	A1	10/2008	Hedner et al.	2012/0058962	A1	3/2012	Cumming et al.
2009/0004246	A1	1/2009	Woolfson et al.	2012/0058979	A1	3/2012	Keith et al.
2009/0010968	A1	1/2009	Allart et al.	2012/0064135	A1	3/2012	Levin et al.
2009/0011041	A1	1/2009	Musaeva et al.	2012/0065179	A1	3/2012	Andersson
2009/0017120	A1	1/2009	Trimble et al.	2012/0065221	A1	3/2012	Babul
2009/0022683	A1	1/2009	Song et al.	2012/0087872	A1	4/2012	Tamarkin et al.
2009/0047357	A1	2/2009	Tomohira et al.	2012/0101073	A1	4/2012	Mannion et al.
2009/0060997	A1	3/2009	Seitz et al.	2012/0121517	A1	5/2012	Song et al.
2009/0081206	A1	3/2009	Leibovitz	2012/0121692	A1	5/2012	Xu et al.
2009/0093440	A1	4/2009	Murad	2012/0122829	A1	5/2012	Taravella et al.
2009/0098069	A1	4/2009	Vacca	2012/0128654	A1	5/2012	Terpstra et al.
2009/0099149	A1	4/2009	Liu et al.	2012/0128683	A1	5/2012	Shantha
2009/0130029	A1	5/2009	Tamarkin et al.	2012/0128733	A1	5/2012	Perrin et al.
2009/0164341	A1	6/2009	Sunvold et al.	2012/0129773	A1	5/2012	Geier et al.
2009/0175799	A1	7/2009	Tamarkin et al.	2012/0129819	A1	5/2012	Vancaillie et al.
2009/0186081	A1	7/2009	Holm et al.	2012/0136013	A1	5/2012	Li et al.
2009/0197843	A1	8/2009	Notelovitz et al.	2012/0142645	A1	6/2012	Marx
2009/0203658	A1	8/2009	Marx et al.	2012/0148670	A1	6/2012	Kim et al.
2009/0227550	A1	9/2009	Mattern	2012/0172343	A1	7/2012	Lindenthal et al.
2009/0285869	A1	11/2009	Trimble	2012/0184515	A1	7/2012	Klar et al.
2009/0324714	A1	12/2009	Liu et al.	2012/0231052	A1	9/2012	Sitruk Ware et al.
2010/0008985	A1	1/2010	Pellikaan et al.	2012/0232011	A1	9/2012	Kneissel et al.
2010/0034838	A1	2/2010	Staniforth et al.	2012/0232042	A1	9/2012	Klar et al.
2010/0034880	A1	2/2010	Sintov et al.	2012/0263679	A1	10/2012	Marlow et al.
2010/0055138	A1	3/2010	Margulies et al.	2012/0277249	A1	11/2012	Andersson et al.
2010/0086501	A1	4/2010	Chang et al.	2012/0277727	A1	11/2012	Doshi et al.
2010/0119585	A1	5/2010	Hille et al.	2012/0295911	A1	11/2012	Mannion et al.
2010/0143420	A1	6/2010	Shenoy et al.	2012/0301517	A1	11/2012	Zhang et al.
2010/0143481	A1	6/2010	Shenoy et al.	2012/0301538	A1	11/2012	Gordon Beresford et al.
2010/0150993	A1	6/2010	Theobald et al.	2012/0302535	A1	11/2012	Caufriez et al.
2010/0204326	A1	8/2010	D Souza	2012/0316130	A1	12/2012	Hendrix
2010/0210994	A1	8/2010	Zarif	2012/0316496	A1	12/2012	Hoffmann et al.
2010/0221195	A1	9/2010	Tamarkin et al.	2012/0321579	A1	12/2012	Edelson et al.
2010/0227797	A1	9/2010	Axelsson et al.	2012/0322779	A9	12/2012	Voskuhl
2010/0247482	A1	9/2010	Cui et al.	2012/0328549	A1	12/2012	Edelson et al.
2010/0247635	A1	9/2010	Rosenberg et al.	2012/0329738	A1	12/2012	Liu
2010/0273730	A1	10/2010	Hsu et al.	2013/0004619	A1	1/2013	Chow et al.
2010/0278759	A1	11/2010	Murad	2013/0011342	A1	1/2013	Tamarkin et al.
2010/0279988	A1	11/2010	Setiawan et al.	2013/0017239	A1	1/2013	Viladot Petit et al.
2010/0291191	A1	11/2010	Shoichet et al.	2013/0023505	A1	1/2013	Garfield et al.
2010/0292199	A1	11/2010	Leverd et al.	2013/0023823	A1	1/2013	Simpson et al.
2010/0322884	A1	12/2010	Dipietro et al.	2013/0028850	A1	1/2013	Tamarkin et al.
2011/0039814	A1	2/2011	Huatan et al.	2013/0029957	A1	1/2013	Giliyar et al.
2011/0066473	A1	3/2011	Bernick et al.	2013/0045266	A1	2/2013	Choi et al.
2011/0087192	A1	4/2011	Uhland et al.	2013/0045953	A1	2/2013	Sitruk Ware et al.
2011/0098258	A1	4/2011	Masini Eteve et al.	2013/0059795	A1	3/2013	Lo et al.
2011/0104268	A1	5/2011	Pachot et al.	2013/0064897	A1	3/2013	Binay
2011/0130372	A1	6/2011	Agostinacchio et al.	2013/0072466	A1	3/2013	Choi et al.
2011/0142945	A1	6/2011	Chen et al.	2013/0084257	A1	4/2013	Ishida et al.
2011/0152840	A1	6/2011	Lee et al.	2013/0085123	A1	4/2013	Li et al.
2011/0158920	A1	6/2011	Morley et al.	2013/0089574	A1	4/2013	Schmidt Gollwitzer et al.
2011/0171140	A1	7/2011	Illum et al.	2013/0090318	A1	4/2013	Ulmann et al.
2011/0190201	A1	8/2011	Hyde et al.	2013/0102781	A1	4/2013	Bevill et al.
2011/0195031	A1	8/2011	Du	2013/0108551	A1	5/2013	Langereis et al.
2011/0238003	A1	9/2011	Bruno Raimondi et al.	2013/0116215	A1	5/2013	Coma et al.
2011/0244043	A1	10/2011	Xu et al.	2013/0116222	A1	5/2013	Arnold et al.
2011/0250256	A1	10/2011	Hyun Oh et al.	2013/0122051	A1	5/2013	Abidi et al.
2011/0250259	A1	10/2011	Buckman	2013/0123175	A1	5/2013	Hill et al.
2011/0262373	A1	10/2011	Umbert Millet	2013/0123220	A1	5/2013	Queiroz
2011/0275584	A1	11/2011	Wilckens et al.	2013/0123351	A1	5/2013	Dewitt
2011/0281832	A1	11/2011	Li et al.	2013/0131027	A1	5/2013	Pakkalin et al.
2011/0287094	A1	11/2011	Penhasi et al.	2013/0131028	A1	5/2013	Snyder et al.
2011/0294738	A1	12/2011	Ren et al.	2013/0131029	A1	5/2013	Bakker et al.
2011/0300167	A1	12/2011	McMurry et al.	2013/0149314	A1	6/2013	Bullerdiek et al.
2011/0301087	A1	12/2011	McBride et al.	2013/0164225	A1	6/2013	Tamarkin et al.
2011/0306579	A1	12/2011	Stein	2013/0164346	A1	6/2013	Lee et al.
2011/0318405	A1	12/2011	Erwin	2013/0165744	A1	6/2013	Carson et al.
2011/0318431	A1	12/2011	Gulati	2013/0178452	A1	7/2013	King
				2013/0183254	A1	7/2013	Zhou et al.
				2013/0183325	A1	7/2013	Bottoni et al.
				2013/0189193	A1	7/2013	Tamarkin et al.
				2013/0189196	A1	7/2013	Tamarkin et al.



## US 9,114,146 B2

Page 5

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2013/0189230 A1 7/2013 Shoichet et al.  
 2013/0189368 A1 7/2013 Mosqueira et al.  
 2013/0210709 A1 8/2013 McMurry et al.  
 2013/0216550 A1 8/2013 Penninger et al.  
 2013/0216596 A1 8/2013 Viladot Petit et al.  
 2013/0224177 A1 8/2013 Kim et al.  
 2013/0224257 A1 8/2013 Sah et al.  
 2013/0224268 A1 8/2013 Alam et al.  
 2013/0224300 A1 8/2013 Maggio  
 2013/0225412 A1 8/2013 Sardari Lodriche et al.  
 2013/0225542 A1 8/2013 Poegh et al.  
 2013/0226113 A1 8/2013 Schumacher et al.  
 2013/0243696 A1 9/2013 Wang et al.  
 2013/0245253 A1 9/2013 Marx et al.  
 2013/0245570 A1 9/2013 Jackson  
 2013/0261096 A1 10/2013 Merian et al.  
 2013/0266645 A1 10/2013 Becker et al.  
 2013/0267485 A1 10/2013 Da Silva Maia Filho  
 2013/0273167 A1 10/2013 Lee et al.  
 2013/0274211 A1 10/2013 Burman et al.  
 2013/0280213 A1 10/2013 Voskuhl  
 2013/0316374 A1 11/2013 Penninger et al.  
 2013/0317065 A1 11/2013 Tatani et al.  
 2013/0317315 A1 11/2013 Lu et al.  
 2013/0324565 A1 12/2013 Li et al.  
 2013/0331363 A1 12/2013 Li et al.  
 2013/0338124 A1 12/2013 Li et al.  
 2013/0345187 A1 12/2013 Rodriguez Oquendo  
 2014/0018335 A1 1/2014 Tatani et al.  
 2014/0024590 A1 1/2014 Weidhaas et al.  
 2014/0031289 A1 1/2014 Song et al.  
 2014/0031323 A1 1/2014 Perez  
 2014/0066416 A1 3/2014 Leunis et al.  
 2014/0072531 A1 3/2014 Kim et al.  
 2014/0079686 A1 3/2014 Barman et al.  
 2014/0088058 A1 3/2014 Maurizio  
 2014/0088059 A1 3/2014 Perumal et al.  
 2014/0094426 A1 4/2014 Drummond et al.  
 2014/0100159 A1 4/2014 Conrad  
 2014/0100206 A1 4/2014 Bernick et al.  
 2014/0113889 A1 4/2014 Connor et al.  
 2014/0127185 A1 5/2014 Stein et al.  
 2014/0127280 A1 5/2014 Duesterberg et al.  
 2014/0127308 A1 5/2014 Opara et al.  
 2014/0128798 A1 5/2014 Janson et al.  
 2014/0148491 A1 5/2014 Valia et al.  
 2014/0186332 A1 7/2014 Ezrin et al.  
 2014/0187487 A1 7/2014 Shoichet et al.  
 2014/0193523 A1 7/2014 Henry  
 2014/0194396 A1 7/2014 Li et al.  
 2014/0206616 A1 7/2014 Ko et al.  
 2014/0371184 A1 12/2014 Bernick et al.  
 2015/0031654 A1 1/2015 Amadio  
 2015/0045335 A1 2/2015 Bernick et al.  
 2015/0133421 A1 5/2015 Bernick et al.

## FOREIGN PATENT DOCUMENTS

WO WO03028667 4/2003  
 WO WO2004014432 2/2004  
 WO WO2005081825 9/2005  
 WO WO2007120868 10/2007  
 WO WO2010146872 12/2010  
 WO WO2012055814 A1 5/2012  
 WO WO2012055840 A1 5/2012  
 WO WO2012065740 5/2012  
 WO WO2012098090 A1 7/2012  
 WO WO2012116277 A1 8/2012  
 WO WO2012118563 A2 9/2012  
 WO WO2012120365 A1 9/2012  
 WO WO2012127501 A2 9/2012  
 WO WO2012156561 A1 11/2012  
 WO WO2012156822 A1 11/2012  
 WO WO2012158483 A2 11/2012

WO WO2012166909 A1 12/2012  
 WO WO2012170578 12/2012  
 WO WO2012170578 A1 12/2012  
 WO WO2013011501 A1 1/2013  
 WO WO2013025449 A1 2/2013  
 WO WO2013028639 A1 2/2013  
 WO WO2013035101 A1 3/2013  
 WO WO2013044067 A1 3/2013  
 WO WO2013045404 A2 4/2013  
 WO WO2013059285 A1 4/2013  
 WO WO2013063279 A1 5/2013  
 WO WO2013064620 A1 5/2013  
 WO WO2013071281 A1 5/2013  
 WO WO2013088254 6/2013  
 WO WO2013102665 A1 7/2013  
 WO WO2013106437 A1 7/2013  
 WO WO2013113690 8/2013  
 WO WO2013124415 A1 8/2013  
 WO WO2013127727 A1 9/2013  
 WO WO2013127728 A1 9/2013  
 WO WO2013144356 A1 10/2013  
 WO WO2013149258 A2 10/2013  
 WO WO2013158454 A2 10/2013  
 WO WO2013170052 A1 11/2013  
 WO 2013192248 12/2013  
 WO 2013192249 12/2013  
 WO 2013192250 12/2013  
 WO 2013192251 12/2013  
 WO WO2013178587 A1 12/2013  
 WO WO2013181449 A1 12/2013  
 WO WO2014001904 A1 1/2014  
 WO WO2014004424 A1 1/2014  
 WO WO2014009434 A1 1/2014  
 WO WO2014018569 A1 1/2014  
 WO WO2014018570 A1 1/2014  
 WO WO2014018571 A2 1/2014  
 WO WO2014018856 A1 1/2014  
 WO WO2014018932 A1 1/2014  
 WO WO2014018932 A2 1/2014  
 WO WO2014031958 A1 2/2014  
 WO WO2014041120 A1 3/2014  
 WO WO2014052792 A1 4/2014  
 WO WO2014056897 A1 4/2014  
 WO WO2014066442 A2 5/2014  
 WO WO2014074846 A1 5/2014  
 WO WO2014076231 A1 5/2014  
 WO WO2014076569 A2 5/2014  
 WO WO2014081598 A1 5/2014  
 WO WO2014086739 A1 6/2014  
 WO WO2014093114 A1 6/2014  
 WO WO2014104784 A1 7/2014

## OTHER PUBLICATIONS

Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.  
 Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.  
 Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," *Clinical Pharmacy*, 1990, vol. 9, No. 5, pp. 366-371.  
 Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," *Journal of Pharmaceutical Sciences*, vol. 86, No. 1, Jan. 1997, pp. 13-18.  
 Sasol Olefins & Surfactants GmbH, Excipients for Pharmaceuticals, 2010, 28 pages.  
 Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," *Food and Chemical Toxicology*, 72 (2014) pp. 40-50.  
 Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," *Journal of Pharmaceutical Sciences*, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.  
 ZRT Laboratory, Provider Data Sheet, About Dried Blood Spot Testing, 2014, 3 pages.  
 Abbas et al., Regression of endometrial implants treated with vitamin D3 in a rat model of endometriosis, *European J of Pharma*, 715 (2013) 72-75, Elsevier.

## US 9,114,146 B2

Page 6

(56)

## References Cited

## OTHER PUBLICATIONS

- Alvarez et al., Ectopic uterine tissue as a chronic pain generator, *Neuroscience*, Dec. 6, 2012, 225: 269-272.
- Application Note FT-IR: JI-Ap-FT0508-008, CD spectra of pharmaceutical substances—Steroids (2), JASCO International Co., Ltd., 2 pages.
- Archer et al., Effects of ospemifene on the female reproductive and urinary tracts: translation from preclinical models into clinical evidence, *Menopause: The Journal of the North American Menopause Society*, vol. 22, No. 77, pp. 1-11 (2015).
- Archer et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study, *Advances in Therapy®*, vol. 9 No. 1, Jan./Feb. 1992.
- Ashburn et al., Cardiovascular, Hepatic and Renal Lesions in Mice Receiving Cortisone, Estrone and Progesterone, *Yale J Biology and Medicine*, vol. 35, Feb. 1963, pp. 329-340.
- Bartosova, Transdermal Drug Delivery In Vitro Using Diffusion Cells, *Current Medicinal Chemistry*, 2012, 19, 4671-4677, Bentham Science Publishers.
- Benbow et al., Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus during Rat Pregnancy, *Biology of Reproduction* 52, 1327-1333 (1995).
- Blake et al., Single and multidose pharmacokinetic study of a vaginal micronized progesterone insert (Endometrin) compared with vaginal gel in healthy reproductive aged female subjects, *Fertility and Sterility®* vol. 94, No. 4, Sep. 2010, Elsevier.
- Christen et al., Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin, *J Clin Oncol* 11:2417-2426, 1993.
- Christensson et al., Limonene hydroperoxide analogues differ in allergenic activity, *Contact Dermatitis* 2008; 59: 344-352.
- Christensson et al., Limonene hydroperoxide analogues show specific patch test reactions, *Contact Dermatitis*, 70, 291-299, 2014.
- Christensson et al., Positive patch test reactions to oxidized limonene: exposure and relevance, *Contact Dermatitis*, 71, 264-272, 2014.
- Cicinelli et al., Direct Transport of Progesterone From Vagina to Uterus, *Obstetrics & Gynecology*, vol. 95, No. 3, Mar. 2000, pp. 403-406.
- Critchley et al., Estrogen Receptor  $\beta$ , But Not Estrogen Receptor  $\alpha$ , Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium, *The Journal of Clinical Endocrinology & Metabolism*, 2001, vol. 86, No. 3, pp. 1370-1378.
- Du et al., Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood, *Menopause: The Journal of the North American Menopause Society*, 2013, vol. 20, No. 11, pp. 1-7.
- Engelhardt et al., Conceptus Influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy, *Biology of Reproduction* 66, 1875-1880 (2002).
- Ettinger et al., Comparison of endometrial growth produced by unopposed conjugated estrogens or by micronized estradiol in postmenopausal women, *Am J Obstet Gynecol* 1997; 176:112-117.
- Filipsson et al., Concise International Chemical Assessment Document 5: Limonene, first draft, World Health Organization, Geneva, 1998, 36 pages.
- Final Report on the Safety Assessment of BHT, *International Journal of Toxicology*, 21(Suppl. 2):19-94, 2002/.
- Flyvholm, Sensitizing risk of butylated hydroxytoluene based on exposure and effect data, *Contact Dermatitis* 1990: 23: 341-345.
- Franklin et al., Characterization of immunoglobulins and cytokines in human cervical mucus: influence of exogenous and endogenous hormones, *Journal of Reproductive Immunology* 42 (1999) 93-106, Elsevier.
- Franz et al., Use of Excised Human Skin to Assess the Bioequivalence of Topical Products, *Skin Pharmacol Physiol* 2009;22:276-286.
- Furness et al., Hormone therapy in postmenopausal women and risk of endometrial hyperplasia (Review), 2012, pp. 1-204, The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
- Gälfvert et al., Free radicals in antigen formation: reduction of contact allergic response to hydroperoxides by epidermal treatment with antioxidants, *British Journal of Dermatology* 2002; 146: 649-656.
- Gattefossé, "Excipients for Safe and Effective Topical Delivery, Drug Development and Delivery" Jul./Aug. 2012, <http://drug-dev.com/Main/Back-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#>.
- Geelen, Math J.H. et al., "Dietary medium-chain fatty acids raise and (n-3) polyunsaturated fatty acids lower hepatic triacylglycerol synthesis in rats," *The Journal of Nutrition*, 1995, 125(10):2449-2456.
- Gillet et al., Induction of amenorrhea during hormone replacement therapy: optimal micronized progesterone dose. A multicenter study, *Maturitas* 19 (1994) 103-115.
- Glaser et al, Pilot Study: Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina, *Gynecol Obstet Invest* 2008;66:111-118.
- Golotowski et al., Comparative evaluation of saliva collection methods for proteome analysis, *Clinica Chimica Acta* 419 (2013) 42-46.
- Graham et al, Physiological Action of Progesterone in Target Tissues, *Endocrine Reviews*, 1997, vol. 18, No. 4, pp. 502-519.
- Groothuis et al., Estrogen and the endometrium: lessons learned from gene expression profiling in rodents and human, *Human Reproduction Update*, vol. 13, No. 4 pp. 405-417, 2007.
- Hamid et al., The effects of common solubilizing agents on the intestinal membrane barrier functions and membrane toxicity in rats, *International Journal of Pharmaceutics* 379 (2009) 100-108, Elsevier.
- He et al., Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia Induced by Ovariectomy Combined with Estrogen, *Gynecol Obstet Invest* 2013;76:51-56.
- Helmy et al., Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats, *Clinic Pharmacol Biopharmaceut*, 2014, S2, 7 pages.
- Herman, Anna et al., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," 2014 Royal Pharmaceutical Society, *Journal of Pharmacy and Pharmacology*, pp. 1-13.
- Hostynek, JJ, Predicting absorption of fragrances hemically through human skin, *J. Soc. Cosm. Chem.*, 46, 221-229 (Jul./Aug. 1995).
- Hurn et al., Estrogen as a Neuroprotectant in Stroke, *Journal of Cerebral Blood Flow and Metabolism* 20:631-652, 2000, Lippincott Williams & Wilkins, Inc., Philadelphia.
- Hyder et al., Synthetic Estrogen 17 $\alpha$ -Ethinyl Estradiol Induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17 $\beta$ -Estradiol, *JPET* 290(2):740-747, 1999.
- Joshi et al., Detection and synthesis of a progestagen-dependent protein in human endometrium, *J Reprod Fert* (1980) 59, 273-285.
- Kanno et al., The OECD Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses: Phase I, *Environmental Health Perspectives* • vol. 109 | No. 8 | Aug. 2001, pp. 785-794.
- Karlberg et al., Air oxidation of d-limonene (the citrus solvent) creates potent allergens, *Contact Dermatitis*, 1992; 26: 332-340.
- Karlberg et al., Influence of an anti-oxidant on the formation of allergenic compounds during auto-oxidation of d-limonene, *Ann. Occup. Hyg.*, vol. 38, No. 2, pp. 199-207, 1994.
- Kaunitz, Andrew M., Extended duration use of menopausal hormone therapy, *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 6, pp. 1-3.
- Kharode et al., The Pairing of a Selective Estrogen Receptor Modulator, Bazedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention, *Endocrinology* 149(12):6084-6091, 2008.
- Kim et al., Safety Evaluation and Risk Assessment of d-Limonene, *Journal of Toxicology and Environmental Health, Part B: Critical Reviews*, 2013, 16:1, 17-38 <http://dx.doi.org/10.1080/10937404.2013.769418>.
- Koga et al., Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate, *European Journal of Pharmaceutics and Biopharmaceutics* 64 (2006) 82-91.



## US 9,114,146 B2

Page 7

(56)

## References Cited

## OTHER PUBLICATIONS

- Komm et al., Bazedoxifene Acetate: A Selective Estrogen Receptor Modulator with Improved Selectivity, *Endocrinology* 146(9):3999-4008, 2005.
- Kumasaka et al., Effects of Various Forms of Progestin on the the Estrogen-Primed, Ovariectomized Rat, *Endocrine Journal* 1994, 41(2), 161-169.
- Kuon et al., A Novel Optical Method to Assess Cervical Changes during Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor, *Am J Obstet Gynecol.* Jul. 2011 ; 205(1): 82.e15-82.e20.
- Kuon et al., Actions of progestins for the inhibition of cervical ripening and uterine contractions to prevent preterm birth, *FVV IN OBGYN*, 2012, 4 (2): 110-119.
- Kuon et al., Pharmacological actions of progestins to inhibit cervical ripening and prevent delivery depend upon their properties, the route of administration and the vehicle, *Am J Obstet Gynecol.* May 2010 ; 202(5): 455.e1-455.e9.
- Leonetti et al., Transdermal progesterone cream as an alternative progestin in hormone therapy, *Alternative Therapies*, Nov./Dec. 2005, vol. 11, No. 6, pp. 36-38.
- López-Belmonte, Corrigendum to "Comparative uterine effects on ovariectomized rats after repeated treatment with different vaginal estrogen formulations" [Maturitas 72 (2012) 353-358], *Maturitas* 74 (2013) 393, Elsevier.
- Madishetti et al., Development of domperidone bilayered matrix type transdermal patches: physicochemical, in vitro and ex vivo characterization, *DARU* vol. 18, No. 3, 2010, pp. 221-229.
- Manson, JoAnn E. et al., "Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials," *JAMA*, Oct. 2, 2013, vol. 310, No. 13, pp. 1353-1368.
- Miles et al., Pharmacokinetics and endometrial tissue levels of progesterone after administration by Intramuscular and vaginal routes: a comparative study, *Fertility and Sterility*, vol. 62, No. 3, Sep. 1994, pp. 485-490.
- Miller et al., Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast, *Journal of Cancer Therapy*, 2012, 3, 749-754.
- Nilsson et al., Analysis of Contact Allergenic Compounds in Oxidized d-Limonene, *Chromatographia* vol. 42, No. 3/4, Feb. 1996, pp. 199-205.
- Opinion on the Diethylene Glycol Monoethyl Ether (DEGEE), Scientific Committee on Consumer Products, Dec. 19, 2006, 27 pages.
- Otterson, K., The Drug Quality and Security Act—Mind the Gaps, *n engl j med* 370;2 nejm.org Jan. 9, 2014, pp. 97-99.
- Palamakula et al., Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components, *Pharmaceutical Technology* Oct. 2004, pp. 74-88.
- Parasuraman et al., Blood sample collection in small laboratory animals, *Journal of Pharmacology & Pharmacotherapeutics* | Jul.-Dec. 2010 | vol. 1 | Issue 2, pp. 87-93.
- Pfaus et al., Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist, *PNAS*, Jul. 6, 2004, vol. 101, No. 27, pp. 10201-10204.
- Pickles, VR, Cutaneous reactions to injection of progesterone solutions into the skin, *Br Med Journal*, Aug. 16, 1952, pp. 373-374.
- Pinkerton et al., What are the concerns about custom-compounded "bioidentical" hormone therapy? *Menopause: The Journal of the North American Menopause Society*, vol. 21, No. 12, 2014, pp. 1-3.
- Portman, David et al., One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy, *Menopause*, vol. 22, No. 11, 2015, pp. 000/000 (8 pages).
- Prausnitz et al., Transdermal drug delivery, *Nat Biotechnol.* Nov. 2008 ; 26(11): 1261-1268.
- Product Safety Assessment: Diethylene Glycol Monoethyl Ether, Created: Sep. 24, 2007 The Dow Chemical Company Page, 5 pages.
- Rahn et al., Vaginal Estrogen for Genitourinary Syndrome of Menopause A Systematic Review, *Obstet Gynecol* 2014;124(6):1147-56.
- Rao, Rajeswara et al., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *J Bioequiv Availab.* 2014, 6: 139-143.
- Reisman et al., Topical Application of the Synthetic Triterpenoid RTA 408 Protects Mice from Radiation-Induced Dermatitis, *Radiation Research* 181,512-520 (2014).
- Ross et al., Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women, *AnnJ Obstet Gynecol*, Oct. 1997, vol. 177, No. 4, pp. 937-941.
- Ruan et al., Systemic progesterone therapy—Oral, vaginal, injections and even transdermal? *Maturitas* 79 (2014) 248-255, Elsevier.
- Salem, HF, Sustained-release progesterone nanosuspension following intramuscular injection in ovariectomized rats, *International Journal of Nanomedicine* 2010;5 943-954, Dove Press.
- Santen, RJ, Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels, *CLIMACTERIC* 2014;17:1-14.
- Schindler, Aldof E. et al., Classification and pharmacology of progestins, *Maturitas* 46S1 (2003) S7-S16.
- Schutte et al., A tissue engineered human endometrial stroma that responds to cues for secretory differentiation, decidualization and menstruation, *Fertil Steril.* Apr. 2012 ; 97(4): 997-1003, Elsevier.
- Schweikart et al., Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats, *Toxicologic Pathology*, 42: 1188-1196, 2014.
- Shao et al., Review Open Access Direct effects of metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma, *Journal of Experimental & Clinical Cancer Research* 2014, 33(1):41, 11 pages.
- Stew, Adeline, moderator, Bioavailability Enhancement with Lipid-Based Drug-Delivery Systems, *Pharmaceutical Technology*, Aug. 2014, pp. 28, 30-31.
- Simon, James A., What if the Women's Health Initiative had used transdermal estradiol and oral progesterone instead? *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 7, pp. 1-15.
- Sitruk-Ware, Regine, "Pharmacological profile of progestins," *Maturitas* 47 (2004) 277-283.
- Smyth et al., Summary of Toxicological Data, a 2-Yr Study of Diethylene Glycol Monoethyl Ether in Rats, *Fd Cosmet. Toxicol.* vol. 2, pp. 641-642, 1964.
- Stanczyk et al., Therapeutically equivalent pharmacokinetic profile across three application sites for AG200-15, a novel low-estrogen dose contraceptive patch, *Contraception*, 87 (2013) pp. 744-749.
- Stanczyk, F.Z. et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," *Menopause: The Journal of the North American Menopause Society*, 2005, vol. 12, No. 2, pp. 232-237.
- Stanczyk, F.Z., "All progestins are not created equal," *Steroids* 68 (2003) 879-880.
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective?" *Climacteric* 2014; 17(Suppl 2):8-11.
- Stephenson et al., "Transdermal progesterone: Effects on Menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women," *Int J Pharmaceutical Compounding*, vol. 12, No. 4, Jul./Aug. 2008, pp. 295-304.
- Sun, Jidong, D-Limonene: Safety and Clinical Applications, *Alternative Medicine Review* vol. 12, No. 3, 2007, pp. 259-264.
- Tang et al., Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat, *Biology of Reproduction* 31, 399-413 (1984).
- Tas et al., Comparison of antiproliferative effects of metformin and progesterone on estrogen-induced endometrial hyperplasia in rats, *Gynecol Endocrinol*, Early Online: 1-4, 2013. <http://informahealthcare.com/gye>.
- Thomas, Peter, Characteristics of membrane progesterin receptor alpha (mPRA) and progesterone membrane receptor component 1

**US 9,114,146 B2**

Page 8

(56)

**References Cited****OTHER PUBLICATIONS**

(PGMRC1) and their roles in mediating rapid progestin actions, *Frontiers in Neuroendocrinology* 29 (2008) 292-312.

Ueda et al., Topical and Transdermal Drug Products, *Pharmacoepial Forum*, vol. 35(3) [May-Jun. 2009], 750-754.

U.S. Appl. No. 13/843,362\_Mar. 16, 2015\_Restriction\_Requirement.

U.S. Appl. No. 13/843,428\_Apr. 14, 2015\_Restriction\_Requirement.

U.S. Appl. No. 14/099,545\_Jul. 14, 2014\_Notice\_of\_Allowance.

U.S. Appl. No. 14/099,562\_Mar. 27, 2014\_Non-Final\_Office\_Action.

U.S. Appl. No. 14/099,562\_Jul. 2, 2014\_Final\_Office\_Action.

U.S. Appl. No. 14/099,562\_Dec. 10, 2014\_Notice\_of\_Allowance.

U.S. Appl. No. 14/099,571\_Mar. 28, 2014\_Restriction\_Requirement.

U.S. Appl. No. 14/099,571\_Jul. 15, 2014\_Notice\_of\_Allowance.

U.S. Appl. No. 14/099,582\_Apr. 29, 2014\_Restriction\_Requirement.

U.S. Appl. No. 14/099,582\_Jun. 17, 2014\_Non-Final\_Office\_Action.

U.S. Appl. No. 14/099,582\_Nov. 7, 2014\_Notice\_of\_Allowance.

U.S. Appl. No. 14/099,582\_Jan. 22, 2015\_Notice\_of\_Allowance.

U.S. Appl. No. 14/099,598\_May 13, 2014\_Restriction\_Requirement.

U.S. Appl. No. 14/099,598\_Jul. 3, 2014\_Non-Final\_Office\_Action.

U.S. Appl. No. 14/099,598\_Dec. 10, 2014\_Notice\_of\_Allowance.

U.S. Appl. No. 14/099,612\_Mar. 20, 2014\_Restriction\_Requirement.

U.S. Appl. No. 14/099,612\_Oct. 30, 2014\_Non-Final\_Office\_Action.

U.S. Appl. No. 14/099,612\_Nov. 26, 2014\_Notice\_of\_Allowance.

U.S. Appl. No. 14/099,623\_Jul. 18, 2014\_Non-Final\_Office\_Action.

U.S. Appl. No. 14/099,623\_Dec. 15, 2014\_Notice\_of\_Allowance.

U.S. Appl. No. 14/103,355\_Dec. 8, 2014\_Non-Final\_Office\_Action.

U.S. Appl. No. 14/106,655\_Jul. 3, 2014\_Restriction\_Requirement.

U.S. Appl. No. 14/125,554\_Dec. 5, 2014\_Restriction\_Requirement.

U.S. Appl. No. 14/125,554\_Apr. 14, 2015\_Non-Final\_Office\_Action.

U.S. Appl. No. 14/136,048\_Nov. 4, 2014\_Restriction\_Requirement.

U.S. Appl. No. 14/136,048\_Mar. 12, 2015\_Non-Final\_Office\_Action.

U.S. Appl. No. 14/475,814\_Oct. 1, 2014\_Non-Final\_Office\_Action.

U.S. Appl. No. 14/475,814\_Feb. 13, 2015\_Notice\_of\_Allowance.

U.S. Appl. No. 14/475,864\_Feb. 11, 2014\_Notice\_of\_Allowance.

U.S. Appl. No. 14/475,864\_Oct. 2, 2014\_Non-Final\_Office\_Action.

U.S. Appl. No. 14/521,230\_Dec. 5, 2014\_Restriction\_Requirement.

U.S. Appl. No. 14/521,230\_Feb. 18, 2015\_Non-Final\_Office\_Action.

U.S. Appl. No. 14/624,051\_Apr. 7, 2015\_Non-Final\_Office\_Action.

Voegtline et al., Dispatches from the interface of salivary bioscience and neonatal research, *Frontiers in Endocrinology*, Mar. 2014, vol. 5, article 25, 8 pages.

Waddell et al., Distribution and metabolism of topically applied progesterone in a rat model, *Journal of Steroid Biochemistry & Molecular Biology* 80 (2002) 449-455.

Waddell et al., The Metabolic Clearance of Progesterone in the Pregnant Rat: Absence of a Physiological Role for the Lung, *Biology of Reproduction* 40, 1188-1193 (1989).

Walter et al., The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice, *Reproduction* (2005) 129 765-777.

Weintraub, Arlene, "Women fooled by untested hormones from compounding pharmacies," *Forbes*, Feb. 20, 2015; retrieved online at <http://onforb.es/1LIUm1V> on Feb. 23, 2015, 3 pages.

Wren et al., Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women, *Climacteric*, 2000, 3(3), pp. 155-160. <http://dx.doi.org/10.1080/13697130008500109>.

Wu et al., Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus, *Biology of Reproduction* 69, 1308-1317 (2003).

Zava, David T. et al., Percutaneous absorption of progesterone, *Maturitas* 77 (2014) 91-92, Elsevier.

Zava, David T., Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues, Script, ZRT Laboratory, pp. 4-5. [http://www.zrtlab.com/component/docman/cat\\_view/10-publications?Itemid](http://www.zrtlab.com/component/docman/cat_view/10-publications?Itemid).

\* cited by examiner

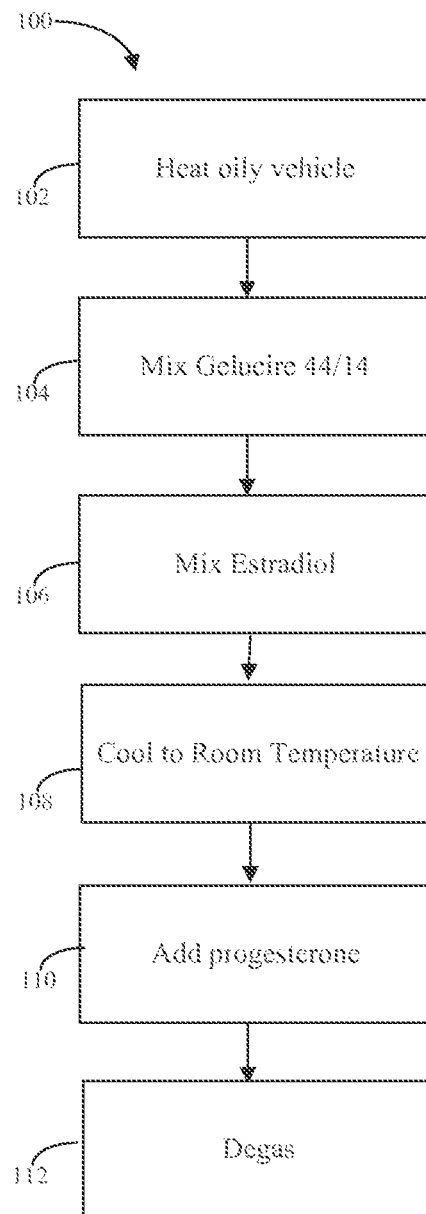
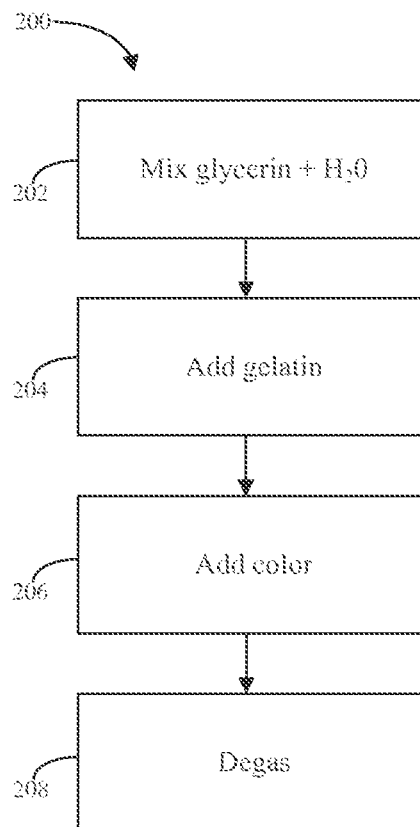
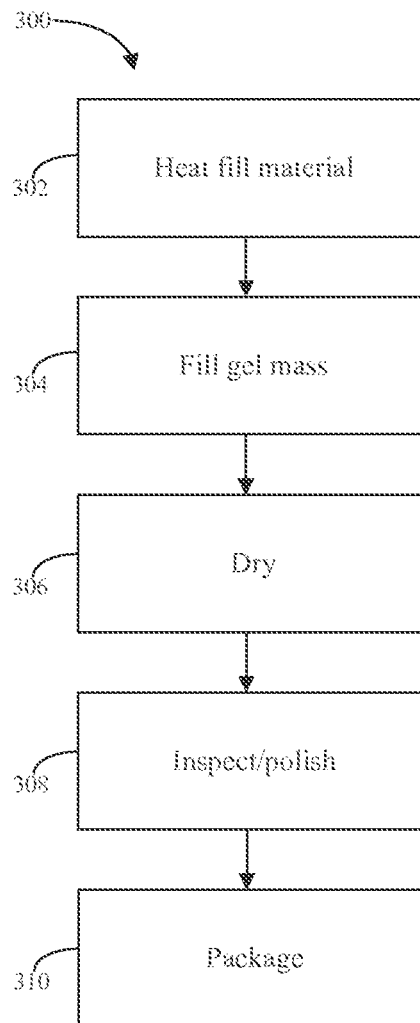


Fig. 1



**Fig. 2**



**Fig. 3**

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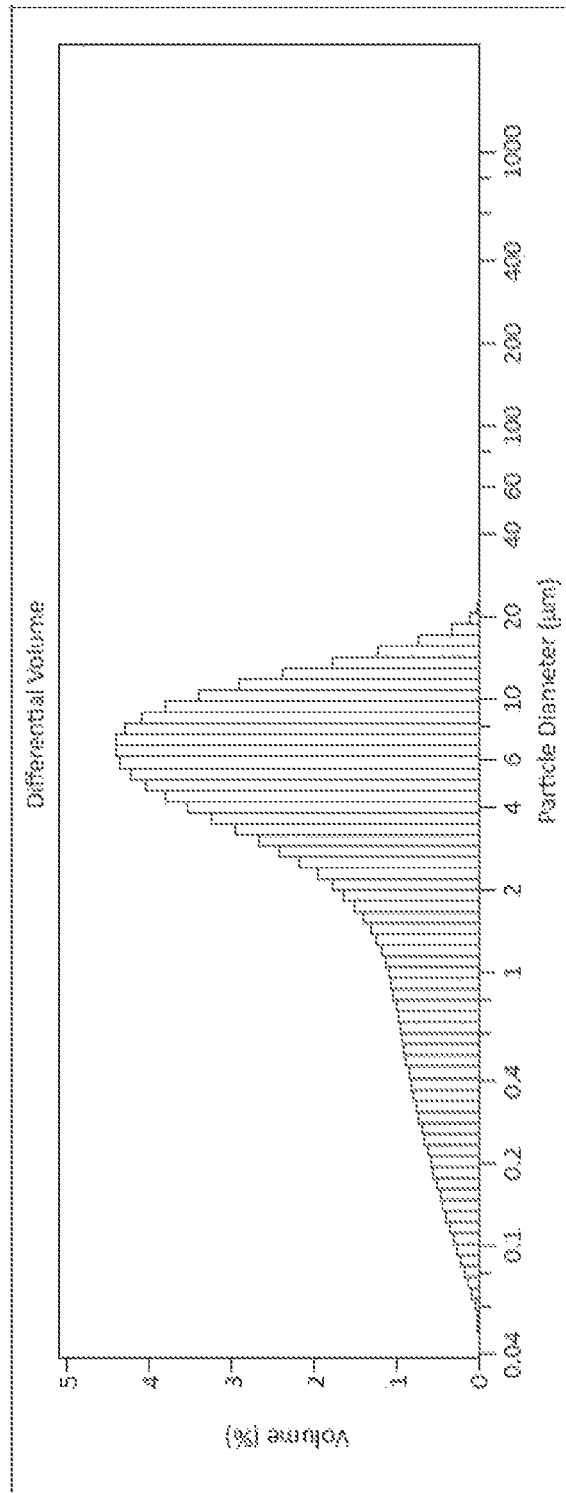


FIG. 4



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## NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

### CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/099,545, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Dec. 6, 2013, which application is a divisional of U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES" which was filed on Nov. 21, 2012 (now U.S. Pat. No. 8,633,178, issued Jan. 21, 2014), which claims priority to the following U.S. Provisional patent applications: U.S. Provisional Application Ser. No. 61/563,408, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES" which was filed on Nov. 23, 2011; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS" which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

### FIELD OF THE INVENTION

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

### BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a

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constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

5 Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

10 "Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

15 These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

20 Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

### SUMMARY OF THE INVENTION

35 According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

### BRIEF DESCRIPTION OF THE DRAWINGS

40 The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

60 FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

65 FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

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## DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

## A. Definitions

The term "micronized progesterone," as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "uniform distribution" means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term "bioavailability," as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC,  $C_{max}$ , and optionally,  $T_{max}$ .

The term "AUC," as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, " $C_{max}$ " as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, " $T_{max}$ " as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC,  $C_{max}$  and, optionally,  $T_{max}$  are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients ("API") substances such as carriers, solvents, oils, lubricants and others used in formulating

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pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "oil" as used herein may be any pharmaceutically acceptable substance, other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

"Fully solubilized progesterone" as used herein means progesterone which is about 100% in solution.

"Partially solubilized progesterone" as used herein means progesterone which is in any state of solubilization up to but not including about 100%.

## B. Description and Preferred Embodiments

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra-

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and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17 $\beta$ -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125,

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1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017  $\mu$ m to 2000  $\mu$ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4  $\mu$ m to 2000  $\mu$ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.



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Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of a caproic fatty acid; a caprylic fatty acid; a capric fatty acid; a tauric acid; a myristic acid; a linoleic acid; a succinic acid; a glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; a propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); a propylene glycol dicaprylate; a propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy) ethanol; Transcutol); a diethylene glycol monoethyl; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Campul MCM; Capmul MCM and a non-ionic surfactant; and Campul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant can be used at ratios including, for example and without limitation: 65:35, 70:30, 75:25, 80:20, 85:15 and 90:10. Campul MCM and Gelucire can be used at ratios including, for example and without limitation, 6:4, 7:3, 8:2, and 9:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In various embodiments, estradiol is partially, substantially or completely solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w).

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other

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solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2, 3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of long chain fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%.

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may

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contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

## EXAMPLES

The following examples are offered to illustrate, but not to limit the claimed invention.

## Example 1

## Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and

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filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

\*Literature reference—Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

## Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various the solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

## Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

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TABLE 3

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:	6	Clear, after 14 days
Capmul PG8 (5:80:15)		
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol:Miglyol:Capmul PG8 are stable and do not precipitate for at least 12 days.

TABLE 4

Formulation	Estradiol mg/g	Results Hot/ Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

## Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

## Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

## Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

## Example 7

## Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.



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As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.

TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

## Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

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For example, Campul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/-2° C. Gelucire 44/14 may be added to the Campul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Campul MCM.

Heat may be removed from the Gelucire 44/14 and Campul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the Gelucire 44/14, Campul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

## Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is

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removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279  $\mu\text{m}$ , an X75 of 7.442  $\mu\text{m}$ , and an X25 of 1.590  $\mu\text{m}$ . The Beckman Device also yielded that the mean particle size is 4.975  $\mu\text{m}$ , the median particle size is 4.279  $\mu\text{m}$ , the mode particle size is 6.453  $\mu\text{m}$ , and the standard deviation is 3.956  $\mu\text{m}$ . A graph of the particle distribution obtained is shown in FIG. 4.

## Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0  $\mu\text{m}$ , an X75 of 17.3  $\mu\text{m}$ , and an X25 of 5.3  $\mu\text{m}$ . The Beckman Device also yielded that the mean particle size is 11.8  $\mu\text{m}$ , the median particle size is 11.04  $\mu\text{m}$ , the mode particle size is 13.6  $\mu\text{m}$ , and the standard deviation is 7.8  $\mu\text{m}$ .

## Example 13

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

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TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

## Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:			100.000	200.00mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	INGREDIENT(S)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until

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dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

#### Example 16

##### Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla.) (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condi-

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tion, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ± 20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

Fasted studies using this protocol were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

#### Example 17

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to 40° C. ± 5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>.

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

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With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Heating may be performed until the temperature reaches 80° C.±5° C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.±3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.±10° C. The wedge temperature may be 38° C.±3° C. The drum cooling temperature may be 4° C.±2° C. The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

What is claimed is:

1. A pharmaceutical composition comprising:  
solubilized estradiol;  
suspended progesterone;  
and a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent and the estradiol and progesterone are uniformly dispersed;  
wherein at least about 90% of the estradiol is solubilized in the solubilizing agent;

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and wherein the solubilizing agent comprises predominately a saturated C6-C12 oil.

2. The pharmaceutical composition of claim 1, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

3. The pharmaceutical composition of claim 1, wherein the formulation is formulated as a gelatin capsule.

4. The pharmaceutical composition of claim 1, wherein said estradiol has a dosage strength of at least about 0.125 mg and wherein said progesterone has a dosage strength of at least about 25 mg.

5. The pharmaceutical composition of claim 1, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

6. A pharmaceutical composition comprising:

solubilized estradiol;

suspended progesterone; and

a solubilizing agent, the solubilizing agent comprising predominately a saturated C6-C12 oil;

wherein the estradiol and the suspended progesterone are present in the solubilizing agent, the estradiol and progesterone are uniformly dispersed, and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the estradiol does not precipitate for at least 14 days.

7. The pharmaceutical composition of claim 6, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

8. The pharmaceutical composition of claim 6, wherein the composition is formulated as a gelatin capsule.

9. The pharmaceutical composition of claim 6, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

10. The pharmaceutical composition of claim 6, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

11. A method of treating menopause symptoms in a woman with a uterus comprising:

administering an effective amount of a pharmaceutical composition, the pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent;

wherein each of the estradiol and the suspended progesterone are present in the solubilizing agent, the estradiol and the suspended progesterone are uniformly dispersed and at least about 90% of the estradiol is solubilized in the solubilizing agent; and

wherein the solubilizing agent comprises predominately a saturated C6-C12 oil.

12. The method of claim 11, further comprising partially solubilized progesterone, wherein the partially solubilized progesterone is solubilized in the solubilizing agent.

13. The method of claim 11, wherein the composition is formulated in a gelatin capsule.

14. The method of claim 11, wherein the estradiol has a dosage strength of at least about 0.125 mg and wherein the progesterone has a dosage strength of at least about 25 mg.

15. The method of claim 11, wherein the ratio of progesterone to estradiol is about 24:1, about 25:1, about 96:1, about 100:1, about 192:1, or about 200:1.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 9,114,146 B2  
APPLICATION NO. : 14/476040  
DATED : August 25, 2015  
INVENTOR(S) : Brian A. Bernick et al.

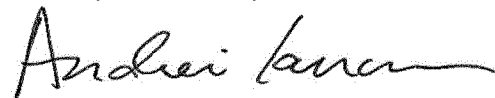
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this  
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu  
*Director of the United States Patent and Trademark Office*

# EXHIBIT J





US009301920B2

(12) **United States Patent**  
**Bernick et al.**

(10) **Patent No.:** **US 9,301,920 B2**  
(45) **Date of Patent:** **\*Apr. 5, 2016**

(54) **NATURAL COMBINATION HORMONE  
REPLACEMENT FORMULATIONS AND  
THERAPIES**

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(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 201 days.

This patent is subject to a terminal dis-  
claimer.

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(60) Provisional application No. 61/661,302, filed on Jun.  
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filed on Jun. 20, 2012.

(51) **Int. Cl.**

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(58) **Field of Classification Search**

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See application file for complete search history.

(56) **References Cited**

#### U.S. PATENT DOCUMENTS

1,967,351	A	7/1934	Dolay
2,232,438	A	2/1941	Butenandt
2,379,832	A	7/1945	Serini et al.
2,649,399	A	8/1953	Beall et al.
3,198,707	A	8/1965	Nomine et al.
3,478,070	A	11/1969	Stein et al.
3,526,648	A	9/1970	Bertin et al.
3,710,795	A	1/1973	Higuchi et al.
3,729,560	A	4/1973	Hagerman
3,729,566	A	4/1973	Ericsson et al.
3,755,573	A	8/1973	Berman
3,755,575	A	8/1973	Lerner
3,903,880	A	9/1975	Higuchi et al.
3,916,898	A	11/1975	Robinson
3,916,899	A	11/1975	Theeuwes et al.
3,921,636	A	11/1975	Zaffaroni
3,923,997	A	12/1975	Meuly
3,948,254	A	4/1976	Zaffaroni
3,971,367	A	7/1976	Zaffaroni
3,977,404	A	8/1976	Theeuwes
3,993,072	A	11/1976	Zaffaroni
4,008,719	A	2/1977	Theeuwes et al.
4,012,496	A	3/1977	Schopflin et al.
4,014,334	A	3/1977	Theeuwes et al.
4,014,987	A	3/1977	Heller et al.
4,016,251	A	4/1977	Higuchi et al.
4,071,623	A	1/1978	van der Vies
4,093,709	A	6/1978	Choi et al.
4,154,820	A	5/1979	Simoons
4,155,991	A	5/1979	Schopflin et al.
4,196,188	A	4/1980	Besins
4,215,691	A	8/1980	Wong
4,237,885	A	12/1980	Wong et al.

(Continued)

#### FOREIGN PATENT DOCUMENTS

BR	PI 1001367-9	A2	7/2012
CN	102258455	A	11/2011

(Continued)

#### OTHER PUBLICATIONS

International Search Report and Written Opinion for PCT/US13/  
46442, dated Nov. 1, 2013.

International Search Report and Written Opinion for PCT/US13/  
46443, dated Oct. 31, 2013.

International Search Report and Written Opinion for PCT/US13/  
46444, dated Oct. 31, 2013.

International Search Report and Written Opinion for PCT/US13/  
46445, dated Nov. 1, 2013.

(Continued)

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#### ABSTRACT

Estrogen and progesterone replacement therapies are pro-  
vided herein. Among others, the following formulations are  
provided herein: solubilized estradiol without progesterone;  
micronized progesterone without estradiol; micronized  
progesterone with partially solubilized progesterone; solubi-  
lized estradiol with micronized progesterone; solubilized  
estradiol with micronized progesterone in combination with  
partially solubilized progesterone; and solubilized estradiol  
with solubilized progesterone.

**14 Claims, 5 Drawing Sheets**

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

4,310,510	A	1/1982	Sherman et al.	5,677,292	A	10/1997	Li et al.
4,327,725	A	5/1982	Cortese et al.	5,686,097	A	11/1997	Taskovich et al.
4,372,951	A	2/1983	Vorys	5,693,335	A	12/1997	Xia et al.
4,384,096	A	5/1983	Sonnabend	5,694,947	A	12/1997	Lehtinen et al.
4,393,871	A	7/1983	Vorhauer et al.	5,700,480	A	12/1997	Hille et al.
4,402,695	A	9/1983	Wong	5,709,844	A	1/1998	Arbeit et al.
4,423,151	A	12/1983	Baranczuk	5,719,197	A	2/1998	Kanios et al.
4,449,980	A	5/1984	Millar et al.	5,735,801	A	4/1998	Caillouette
4,610,687	A	9/1986	Fogwell	5,739,176	A	4/1998	Dunn et al.
4,629,449	A	12/1986	Wong	5,744,463	A	4/1998	Bair
4,732,763	A	3/1988	Beck et al.	5,747,058	A	5/1998	Tipton et al.
4,738,957	A	4/1988	Laurent et al.	5,770,219	A	6/1998	Chiang et al.
4,756,907	A	7/1988	Beck et al.	5,770,220	A	6/1998	Meconi et al.
4,762,717	A	8/1988	Crowley, Jr.	5,770,227	A	6/1998	Dong et al.
4,788,062	A	11/1988	Gale et al.	5,776,495	A	7/1998	Duclos et al.
4,816,257	A	3/1989	Buster et al.	5,780,044	A	7/1998	Yewey et al.
4,822,616	A	4/1989	Zimmermann et al.	5,780,050	A	7/1998	Jain et al.
4,865,848	A	9/1989	Cheng et al.	5,788,980	A	8/1998	Nabahi
4,900,734	A	2/1990	Maxson et al.	5,788,984	A	8/1998	Guenther et al.
4,906,475	A	3/1990	Kim	5,789,442	A	8/1998	Garfield et al.
4,942,158	A	7/1990	Sarpotdar et al.	5,811,416	A	9/1998	Chwalisz et al.
4,961,931	A	10/1990	Wong	5,811,547	A	9/1998	Nakamichi et al.
5,030,629	A	7/1991	Rajadhyaksha	5,814,329	A	9/1998	Shah
5,064,654	A	11/1991	Berner et al.	5,820,878	A	10/1998	Hirano et al.
5,108,995	A	4/1992	Casper	5,827,200	A	10/1998	Caillouette
5,128,138	A	7/1992	Blank	5,840,327	A	11/1998	Gale et al.
5,130,137	A	7/1992	Crowley, Jr.	5,843,468	A	12/1998	Burkoth et al.
5,140,021	A	8/1992	Maxson et al.	5,843,979	A	12/1998	Wille et al.
5,211,952	A	5/1993	Spicer et al.	5,858,394	A	1/1999	Lipp et al.
5,252,334	A	10/1993	Chiang et al.	5,863,552	A	1/1999	Yue
5,280,023	A	1/1994	Ehrlich et al.	5,866,603	A	2/1999	Li et al.
5,288,496	A	2/1994	Lewis	5,882,676	A	3/1999	Lee et al.
5,340,584	A	8/1994	Spicer et al.	5,885,612	A	3/1999	Meconi et al.
5,340,585	A	8/1994	Pike et al.	5,888,533	A	3/1999	Dunn
5,340,586	A	8/1994	Pike et al.	5,891,462	A	4/1999	Carrara
5,362,497	A	11/1994	Yamada et al.	5,891,868	A	4/1999	Cummings et al.
5,382,573	A	1/1995	Casper	5,898,038	A	4/1999	Yallampalli et al.
5,393,528	A	2/1995	Staab	5,902,603	A	5/1999	Chen et al.
5,393,529	A	2/1995	Hoffmann et al.	5,904,931	A	5/1999	Lipp et al.
5,419,910	A	5/1995	Lewis	5,906,830	A	5/1999	Farinas et al.
5,468,736	A	11/1995	Hodgen	5,912,010	A	6/1999	Wille et al.
5,474,783	A	12/1995	Miranda et al.	5,916,176	A	6/1999	Caillouette
5,480,776	A	1/1996	Dullien	RE36,247	E	7/1999	Plunkett et al.
5,514,673	A	5/1996	Heckenmueller et al.	5,919,477	A	7/1999	Bevan et al.
5,516,528	A	5/1996	Hughes et al.	5,922,349	A	7/1999	Elliesen et al.
5,527,534	A	6/1996	Myhling	5,928,666	A	7/1999	Farinas et al.
5,529,782	A	6/1996	Staab	5,942,243	A	8/1999	Shah
5,538,736	A	7/1996	Hoffmann et al.	5,942,531	A	8/1999	Diaz et al.
5,543,150	A	8/1996	Bologna et al.	5,952,000	A	9/1999	Venkateshwaran et al.
5,547,948	A	8/1996	Barcomb	5,958,446	A	9/1999	Miranda et al.
5,556,635	A	9/1996	Istin et al.	5,962,445	A	10/1999	Stewart
5,565,199	A	10/1996	Page et al.	5,968,919	A	10/1999	Samour et al.
5,567,831	A	10/1996	Li	5,972,372	A	10/1999	Saleh et al.
5,569,652	A	10/1996	Beier et al.	5,985,311	A	11/1999	Cordes et al.
5,580,572	A	12/1996	Mikler et al.	5,985,850	A	11/1999	Falk et al.
5,582,592	A	12/1996	Kendrick	5,985,861	A	11/1999	Levine et al.
5,585,370	A	12/1996	Casper	5,989,568	A	11/1999	Breton et al.
5,595,759	A	1/1997	Wright et al.	5,993,856	A	11/1999	Ragavan et al.
5,595,970	A	1/1997	Garfield et al.	6,001,846	A	12/1999	Edwards et al.
5,605,702	A	2/1997	Teillaud et al.	6,007,835	A	12/1999	Bon-Lapillonne et al.
5,607,691	A	3/1997	Hale et al.	6,010,715	A	1/2000	Wick et al.
5,607,693	A	3/1997	Bonte et al.	6,013,276	A	1/2000	Math et al.
5,609,617	A	3/1997	Shealy et al.	6,022,562	A	2/2000	Autant et al.
5,620,705	A	4/1997	Dong et al.	6,024,974	A	2/2000	Li
5,626,866	A	5/1997	Ebert et al.	6,024,976	A	2/2000	Miranda et al.
5,629,021	A	5/1997	Wright	6,028,057	A	2/2000	Burns
5,633,011	A	5/1997	Dong et al.	6,030,948	A	2/2000	Mann
5,633,242	A	5/1997	Oettel et al.	6,039,968	A	3/2000	Nabahi
5,639,743	A	6/1997	Kaswan et al.	6,040,340	A	3/2000	Chwalisz et al.
5,653,983	A	8/1997	Meybeck et al.	6,056,972	A	5/2000	Hermesmeyer
5,656,286	A	8/1997	Miranda et al.	6,060,077	A	5/2000	Meignant
5,660,839	A	8/1997	Allec et al.	6,068,853	A	5/2000	Giannos et al.
5,662,927	A	9/1997	Ehrlich et al.	6,074,625	A	6/2000	Hawthorne et al.
5,663,160	A	9/1997	Meybeck et al.	6,077,531	A	6/2000	Salin-Drouin
5,676,968	A	10/1997	Lipp et al.	6,080,118	A	6/2000	Blythe
				6,083,178	A	7/2000	Caillouette
				6,086,916	A	7/2000	Agnus et al.
				6,087,352	A	7/2000	Trout
				6,090,404	A	7/2000	Meconi et al.

## US 9,301,920 B2

Page 3

(56)

## References Cited

## U.S. PATENT DOCUMENTS

6,096,338 A	8/2000	Lacy et al.	6,521,250 B2	2/2003	Mecconi et al.
6,106,848 A	8/2000	Preuillh et al.	6,526,980 B1	3/2003	Tracy et al.
6,117,446 A	9/2000	Place	6,528,094 B1	3/2003	Savoit et al.
6,117,450 A	9/2000	Dittgen et al.	6,531,149 B1	3/2003	Kirstgen et al.
6,124,362 A	9/2000	Bradbury et al.	6,537,580 B1	3/2003	Savoit et al.
6,133,251 A	10/2000	Dittgen et al.	6,538,039 B2	3/2003	Laurent
6,133,320 A	10/2000	Yallampalli et al.	6,544,196 B2	4/2003	Caillouette
6,139,868 A	10/2000	Hoffmann	6,544,553 B1	4/2003	Hsia et al.
6,139,873 A	10/2000	Hughes, Jr. et al.	6,548,053 B1	4/2003	Stewart et al.
6,149,935 A	11/2000	Chiang et al.	6,548,491 B2	4/2003	Tanabe et al.
6,153,216 A	11/2000	Cordes et al.	6,551,611 B2	4/2003	Elliesen et al.
6,165,491 A	12/2000	Grasset et al.	6,555,131 B1	4/2003	Wolff et al.
6,165,975 A	12/2000	Adams et al.	6,562,367 B1	5/2003	Wolff et al.
6,187,323 B1	2/2001	Aiache et al.	6,562,370 B2	5/2003	Luo et al.
6,187,339 B1	2/2001	de Haan et al.	6,562,790 B2	5/2003	Chein
6,190,331 B1	2/2001	Caillouette	6,569,463 B2	5/2003	Patel et al.
6,201,072 B1	3/2001	Rathi et al.	6,583,129 B1	6/2003	Mazer et al.
6,217,886 B1	4/2001	Onyueksel et al.	6,586,006 B2	7/2003	Roser et al.
6,225,297 B1	5/2001	Stockemann et al.	6,589,549 B2	7/2003	Shih et al.
6,227,202 B1	5/2001	Matapurkar	6,593,317 B1	7/2003	de Ziegler et al.
6,228,383 B1	5/2001	Hansen et al.	6,599,519 B1	7/2003	Seo et al.
6,228,852 B1	5/2001	Shaak	6,610,652 B2	8/2003	Adams et al.
6,242,509 B1	6/2001	Berger et al.	6,610,670 B2	8/2003	Backensfeld et al.
6,245,811 B1	6/2001	Horrobin et al.	6,610,674 B1	8/2003	Schreiber
6,262,115 B1	7/2001	Guittard et al.	6,635,274 B1	10/2003	Masiz et al.
6,267,984 B1	7/2001	Beste et al.	6,638,528 B1	10/2003	Kanios
6,274,165 B1	8/2001	Mecconi et al.	6,638,536 B2	10/2003	Savoit et al.
6,277,418 B1	8/2001	Markaverich et al.	6,645,528 B1	11/2003	Straub et al.
6,283,927 B1	9/2001	Caillouette	6,649,155 B1	11/2003	Dunlop et al.
6,287,588 B1	9/2001	Shih et al.	6,653,298 B2	11/2003	Potter et al.
6,287,693 B1	9/2001	Savoit et al.	6,656,929 B1	12/2003	Agnus et al.
6,294,188 B1	9/2001	Ragavan et al.	6,660,726 B2	12/2003	Hill et al.
6,294,192 B1	9/2001	Patel et al.	6,663,608 B2	12/2003	Rathbone et al.
6,294,550 B1	9/2001	Place et al.	6,663,895 B2	12/2003	Savoit et al.
6,299,900 B1	10/2001	Reed et al.	6,682,757 B1	1/2004	Wright
6,303,132 B1	10/2001	Nelson	6,692,763 B1	2/2004	Cummings et al.
6,303,588 B1	10/2001	Danielov	6,708,822 B1	3/2004	Muni
6,306,841 B1	10/2001	Place et al.	6,720,001 B2	4/2004	Chen et al.
6,306,914 B1	10/2001	de Ziegler et al.	6,737,081 B2	5/2004	Savoit et al.
6,309,669 B1	10/2001	Setterstrom et al.	6,740,333 B2	5/2004	Beckett et al.
6,309,848 B1	10/2001	Howett et al.	6,743,448 B2	6/2004	Kryger
6,312,703 B1	11/2001	Orthoefer	6,743,815 B2	6/2004	Huebner et al.
6,328,987 B1	12/2001	Marini	6,747,018 B2	6/2004	Tanabe et al.
6,342,491 B1	1/2002	Dey et al.	6,750,291 B2	6/2004	Kim et al.
6,344,211 B1	2/2002	Hille	6,756,208 B2	6/2004	Griffin et al.
6,372,209 B1	4/2002	Chrisope	6,776,164 B2	8/2004	Bunt et al.
6,372,245 B1	4/2002	Bowman et al.	6,787,152 B2	9/2004	Kirby et al.
6,372,246 B1	4/2002	Wei et al.	6,805,877 B2	10/2004	Massara et al.
6,387,390 B1	5/2002	Deaver et al.	6,809,085 B1	10/2004	Elson et al.
6,402,705 B1	6/2002	Caillouette	6,818,226 B2	11/2004	Reed et al.
6,416,778 B1	7/2002	Ragavan et al.	6,821,524 B2	11/2004	Marini
6,420,352 B1	7/2002	Knowles	6,841,716 B1	1/2005	Tsutsumi
6,423,039 B1	7/2002	Rathbone et al.	6,844,334 B2	1/2005	Hill et al.
6,423,683 B1	7/2002	Heaton et al.	6,855,703 B1	2/2005	Hill et al.
6,432,438 B1	8/2002	Shukla	6,860,859 B2	3/2005	Mehrotra et al.
6,436,633 B1	8/2002	Kreider et al.	6,866,865 B2	3/2005	Hsia et al.
6,440,454 B1	8/2002	Santoro et al.	6,869,969 B2	3/2005	Huebner et al.
6,444,224 B1	9/2002	Rathbone et al.	6,878,518 B2	4/2005	Whitehead
6,444,234 B1	9/2002	Kirby et al.	6,901,278 B1	5/2005	Notelovitz
6,451,300 B1	9/2002	Dunlop et al.	6,905,705 B2	6/2005	Palm et al.
6,451,339 B2	9/2002	Patel et al.	6,911,211 B2	6/2005	Eini et al.
6,451,779 B1	9/2002	Hesch	6,911,438 B2	6/2005	Wright
6,455,246 B1	9/2002	Howett et al.	6,923,988 B2	8/2005	Patel et al.
6,455,517 B1	9/2002	Tanabe et al.	6,924,274 B2	8/2005	Lardy et al.
6,465,004 B1	10/2002	Rossi Montero et al.	6,932,983 B1	8/2005	Straub et al.
6,465,005 B1	10/2002	Biali et al.	6,939,558 B2	9/2005	Massara et al.
6,465,006 B1	10/2002	Zhang et al.	6,943,021 B2	9/2005	Klausner et al.
6,468,526 B2	10/2002	Chrisope	6,958,327 B1	10/2005	Hillisch et al.
6,469,016 B1	10/2002	Place et al.	6,960,337 B2	11/2005	Daniels et al.
6,472,434 B1	10/2002	Place et al.	6,962,691 B1	11/2005	Lulla et al.
6,479,232 B1	11/2002	Howett et al.	6,962,908 B2	11/2005	Aloba et al.
6,495,160 B2	12/2002	Esposito et al.	6,967,194 B1	11/2005	Matsuo et al.
6,500,814 B1	12/2002	Hesch	6,974,569 B2	12/2005	Dunlop et al.
6,503,896 B1	1/2003	Tanabe et al.	6,977,250 B2	12/2005	Rodriguez
6,511,969 B1	1/2003	Hermesmeier	6,978,945 B2	12/2005	Wong et al.
			6,995,149 B1	2/2006	Endrikat et al.
			7,004,321 B1	2/2006	Palm et al.
			7,005,429 B2	2/2006	Dey et al.
			7,011,846 B2	3/2006	Shojaei et al.

## US 9,301,920 B2

Page 4

(56)

## References Cited

## U.S. PATENT DOCUMENTS

7,018,992 B2	3/2006	Koch et al.	7,867,990 B2	1/2011	Schultz et al.
7,030,104 B2	4/2006	Gray et al.	7,871,643 B2	1/2011	Lizio et al.
7,030,157 B2	4/2006	Ke et al.	7,879,830 B2	2/2011	Wiley
RE39,104 E	5/2006	Duclos et al.	7,884,093 B2	2/2011	Creasy et al.
7,074,779 B2	7/2006	Sui et al.	7,925,519 B2	4/2011	Greene
7,083,590 B1	8/2006	Bunt et al.	7,939,104 B2	5/2011	Barbera et al.
7,091,213 B2	8/2006	Metcalf, III et al.	7,943,602 B2	5/2011	Bunschoten et al.
7,094,228 B2	8/2006	Zhang et al.	7,943,604 B2	5/2011	Coelingh Bennink et al.
7,097,853 B1	8/2006	Garbe et al.	7,945,459 B2	5/2011	Grace et al.
7,101,342 B1	9/2006	Caillouette	7,960,368 B2	6/2011	Nickisch et al.
7,105,573 B2	9/2006	Krajcik et al.	7,989,436 B2	8/2011	Hill et al.
7,135,190 B2	11/2006	Piao et al.	7,989,487 B2	8/2011	Welsh et al.
7,153,522 B1	12/2006	Ikeura et al.	8,022,053 B2	9/2011	Mueller et al.
7,163,681 B2	1/2007	Giles-Komar et al.	8,048,017 B2	11/2011	Xu
7,163,699 B2	1/2007	Besse	8,048,869 B2	11/2011	Bunschoten et al.
7,175,850 B2	2/2007	Cevc	8,063,030 B2	11/2011	Ellman
7,179,799 B2	2/2007	Hill et al.	8,071,576 B2	12/2011	Coelingh Bennink et al.
7,196,074 B2	3/2007	Blye et al.	8,071,729 B2	12/2011	Giles-Komar et al.
7,198,800 B1	4/2007	Ko	8,075,916 B2	12/2011	Song et al.
7,198,801 B2	4/2007	Carrara et al.	8,075,917 B2	12/2011	Chung et al.
7,226,910 B2	6/2007	Wilson et al.	8,076,317 B2	12/2011	Kulmann
7,247,625 B2	7/2007	Zhang et al.	8,076,319 B2	12/2011	Leonard
7,250,446 B2	7/2007	Sangita et al.	8,080,553 B2	12/2011	Keith et al.
7,267,829 B2	9/2007	Kirby et al.	8,088,605 B2	1/2012	Beaudet et al.
7,300,926 B2	11/2007	Prokai et al.	8,096,940 B2	1/2012	Josephson et al.
7,303,763 B2	12/2007	Ho	8,101,209 B2	1/2012	Legrand et al.
7,317,037 B2	1/2008	Fensome et al.	8,114,152 B2	2/2012	Furst
7,329,654 B2	2/2008	Kanojia et al.	8,114,434 B2	2/2012	Sasaki et al.
7,335,650 B2	2/2008	Potter et al.	8,114,442 B2	2/2012	Tucker et al.
7,374,779 B2	5/2008	Chen et al.	8,119,741 B2	2/2012	Pavlin
7,378,404 B2	5/2008	Peters et al.	8,121,886 B2	2/2012	Azar
7,381,427 B2	6/2008	Ancira et al.	8,124,118 B2	2/2012	Lennernaes et al.
7,387,789 B2	6/2008	Klose et al.	8,124,595 B2	2/2012	Boissonneault
7,388,006 B2	6/2008	Schmees et al.	8,147,561 B2	4/2012	Binmoeller
7,414,043 B2	8/2008	Kosemund et al.	8,148,546 B2	4/2012	Schuster et al.
7,427,413 B2	9/2008	Savoir et al.	8,158,613 B2	4/2012	Staniforth et al.
7,427,609 B2	9/2008	Leonard	8,158,614 B2	4/2012	Lambert et al.
7,429,576 B2	9/2008	Labrie	8,163,722 B2	4/2012	Savoir et al.
7,431,941 B2	10/2008	Besins et al.	8,177,449 B2	5/2012	Bayly et al.
7,456,159 B2	11/2008	Houze et al.	8,182,833 B2	5/2012	Hermesmeyer
7,459,445 B2	12/2008	Hill et al.	8,187,615 B2	5/2012	Friedman
7,465,587 B2	12/2008	Imrich	8,187,640 B2	5/2012	Dunn
7,470,433 B2	12/2008	Carrara et al.	8,195,403 B2	6/2012	Ishikawa et al.
7,485,666 B2	2/2009	Villanueva et al.	8,202,736 B2	6/2012	Mousa et al.
7,497,855 B2	3/2009	Ausiello et al.	8,217,024 B2	7/2012	Ahmed et al.
7,498,303 B2	3/2009	Arnold et al.	8,221,785 B2	7/2012	Chien
7,534,765 B2	5/2009	Gregg et al.	8,222,008 B2	7/2012	Thoene
7,534,780 B2	5/2009	Wyrwa et al.	8,222,237 B2	7/2012	Nickisch et al.
7,550,142 B2	6/2009	Giles-Komar et al.	8,227,454 B2	7/2012	Hill et al.
7,563,565 B1	7/2009	Matsuo et al.	8,227,509 B2	7/2012	Castro et al.
7,569,274 B2	8/2009	Besse et al.	8,241,664 B2	8/2012	Dudley et al.
7,572,779 B2	8/2009	Aloba et al.	8,247,393 B2	8/2012	Ahmed et al.
7,572,780 B2	8/2009	Hermesmeyer	8,257,724 B2	9/2012	Cromack et al.
7,589,082 B2	9/2009	Savoir et al.	8,257,725 B2	9/2012	Cromack et al.
7,671,027 B2	3/2010	Loumaye	8,268,352 B2	9/2012	Vaya et al.
7,674,783 B2	3/2010	Hermesmeyer	8,268,806 B2	9/2012	Labrie
7,687,281 B2	3/2010	Roth et al.	8,268,878 B2	9/2012	Armer et al.
7,687,485 B2	3/2010	Levinson et al.	8,273,730 B2	9/2012	Fernandez et al.
7,694,683 B2	4/2010	Callister et al.	8,287,888 B2	10/2012	Song et al.
7,704,983 B1	4/2010	Hodgen et al.	8,288,366 B2	10/2012	Chochinov et al.
7,727,720 B2	6/2010	Dhallan	8,318,898 B2	11/2012	Fasel et al.
7,732,408 B2	6/2010	Josephson et al.	8,324,193 B2	12/2012	Lee Sepsick et al.
7,749,989 B2	7/2010	Hill et al.	8,329,680 B2	12/2012	Evans et al.
7,767,656 B2	8/2010	Shoichet et al.	8,337,814 B2	12/2012	Osbakken et al.
7,799,769 B2	9/2010	White et al.	8,344,007 B2	1/2013	Tang et al.
7,815,936 B2	10/2010	Hasenzahl et al.	8,349,820 B2	1/2013	Zeun et al.
7,815,949 B2	10/2010	Cohen	8,353,863 B2	1/2013	Imran
7,829,115 B2	11/2010	Besins et al.	8,357,723 B2	1/2013	Satyam
7,829,116 B2	11/2010	Griswold et al.	8,361,995 B2	1/2013	Schramm
RE42,012 E	12/2010	Deaver et al.	8,362,091 B2	1/2013	Tamarkin et al.
7,850,992 B2	12/2010	Kim et al.	8,372,424 B2	2/2013	Berry et al.
7,854,753 B2	12/2010	Kraft et al.	8,372,806 B2	2/2013	Boehler et al.
7,858,607 B2	12/2010	Mamchur	8,377,482 B2	2/2013	Laurie et al.
RE42,072 E	1/2011	Deaver et al.	8,377,994 B2	2/2013	Gray et al.
7,862,552 B2	1/2011	McIntyre et al.	8,394,759 B2	3/2013	Barathur et al.
			8,415,332 B2	4/2013	Diliberti et al.
			8,420,111 B2	4/2013	Hermesmeyer
			8,435,561 B2	5/2013	Besins et al.
			8,435,972 B2	5/2013	Stein et al.

## US 9,301,920 B2

Page 5

(56)

## References Cited

## U.S. PATENT DOCUMENTS

8,449,879 B2	5/2013	Laurent Applegate et al.	2002/0058926 A1	5/2002	Rathbone et al.
8,450,108 B2	5/2013	Boyce	2002/0064541 A1	5/2002	Lapidot et al.
8,454,945 B2	6/2013	Mccook et al.	2002/0076441 A1	6/2002	Shih et al.
8,455,468 B2	6/2013	Hoffman et al.	2002/0102308 A1	8/2002	Wei et al.
8,461,138 B2	6/2013	Boissonneault	2002/0107230 A1	8/2002	Waldon et al.
8,476,252 B2	7/2013	Achleitner et al.	2002/0114803 A1	8/2002	Deaver et al.
8,481,488 B2	7/2013	Carter	2002/0119174 A1	8/2002	Gardlik et al.
8,486,374 B2	7/2013	Tamarkin et al.	2002/0119198 A1	8/2002	Gao et al.
8,486,442 B2	7/2013	Matsushita et al.	2002/0132801 A1	9/2002	Heil et al.
8,492,368 B2	7/2013	Vanlandingham et al.	2002/0137749 A1	9/2002	Levinson et al.
8,507,467 B2	8/2013	Matsui et al.	2002/0142017 A1	10/2002	Simonnet
8,512,693 B2	8/2013	Capito et al.	2002/0151530 A1	10/2002	Leonard et al.
8,512,754 B2	8/2013	Needham	2002/0156394 A1	10/2002	Mehrotra et al.
8,518,376 B2	8/2013	Tamarkin et al.	2002/0169150 A1	11/2002	Pickar
8,536,159 B2	9/2013	Li et al.	2002/0169205 A1	11/2002	Chwalisz et al.
8,540,967 B2	9/2013	Barrett et al.	2002/0173510 A1	11/2002	Levinson et al.
8,541,400 B2	9/2013	Johnsson et al.	2002/0193356 A1	12/2002	Van Beek et al.
8,551,462 B2	10/2013	Goldstein et al.	2002/0193758 A1	12/2002	Sandberg
8,557,281 B2	10/2013	Halliday et al.	2002/0197286 A1	12/2002	Brandman et al.
8,568,374 B2	10/2013	De Graaff et al.	2003/0003139 A1	1/2003	Lipp et al.
8,591,951 B2	11/2013	Kohn et al.	2003/0004145 A1	1/2003	Leonard
8,613,951 B2	12/2013	Zale et al.	2003/0007994 A1	1/2003	Bunt et al.
8,633,178 B2	1/2014	Bernick et al.	2003/0027772 A1	2/2003	Breton
8,633,180 B2	1/2014	Li et al.	2003/0044453 A1	3/2003	Dittgen et al.
8,636,787 B2	1/2014	Sabaria	2003/0049307 A1	3/2003	Gyurik
8,636,982 B2	1/2014	Tamarkin et al.	2003/0064097 A1	4/2003	Patel et al.
8,653,129 B2	2/2014	Fein et al.	2003/0072760 A1	4/2003	Sirbasku
8,658,627 B2	2/2014	Voskuhl	2003/0073248 A1	4/2003	Roth et al.
8,658,628 B2	2/2014	Baucom	2003/0073673 A1	4/2003	Hesch
8,663,681 B2	3/2014	Ahmed et al.	2003/0077297 A1	4/2003	Chen et al.
8,663,692 B1	3/2014	Mueller et al.	2003/0078245 A1	4/2003	Bennink et al.
8,663,703 B2	3/2014	Lerner et al.	2003/0091620 A1	5/2003	Fikstad et al.
8,664,207 B2	3/2014	Li et al.	2003/0091640 A1	5/2003	Ramanathan et al.
8,669,293 B2	3/2014	Levy et al.	2003/0092691 A1	5/2003	Besse et al.
8,679,552 B2	3/2014	Guthery	2003/0096012 A1	5/2003	Besse et al.
8,694,358 B2	4/2014	Tryfon	2003/0104048 A1	6/2003	Patel et al.
8,697,127 B2	4/2014	Sah	2003/0109507 A1	6/2003	Franke et al.
8,697,710 B2	4/2014	Li et al.	2003/0113268 A1	6/2003	Buenafoe et al.
8,703,105 B2	4/2014	Tamarkin et al.	2003/0114420 A1	6/2003	Salvati et al.
8,709,385 B2	4/2014	Tamarkin et al.	2003/0114430 A1	6/2003	MacLeod et al.
8,709,451 B2	4/2014	Nam et al.	2003/0124182 A1	7/2003	Shojaei et al.
8,715,735 B2	5/2014	Funke et al.	2003/0124191 A1	7/2003	Besse et al.
8,721,331 B2	5/2014	Raghuprasad	2003/0130558 A1	7/2003	Massara et al.
8,722,021 B2	5/2014	Friedman et al.	2003/0144258 A1	7/2003	Heil et al.
8,734,846 B2	5/2014	Ali et al.	2003/0157157 A1	8/2003	Luo et al.
8,735,381 B2	5/2014	Podolski	2003/0166509 A1	9/2003	Edwards et al.
8,741,336 B2	6/2014	Dipierro et al.	2003/0170295 A1	9/2003	Kim et al.
8,741,373 B2	6/2014	Bromley et al.	2003/0175329 A1	9/2003	Azarnoff et al.
8,753,661 B2	6/2014	Steinmueller Nethl et al.	2003/0175333 A1	9/2003	Shefer et al.
8,784,882 B2	7/2014	Mattern	2003/0180352 A1	9/2003	Patel et al.
8,846,648 B2	9/2014	Bernick et al.	2003/0181353 A1	9/2003	Nyce
8,846,649 B2	9/2014	Bernick et al.	2003/0181728 A1	9/2003	Salvati et al.
8,933,059 B2	1/2015	Bernick et al.	2003/0191096 A1	10/2003	Leonard et al.
8,987,237 B2	3/2015	Bernick et al.	2003/0195177 A1	10/2003	Leonard et al.
8,987,238 B2	3/2015	Bernick et al.	2003/0215496 A1	11/2003	Patel et al.
8,993,548 B2	3/2015	Bernick et al.	2003/0219402 A1	11/2003	Rutter
8,993,549 B2	3/2015	Bernick et al.	2003/0220297 A1	11/2003	Berstein et al.
9,006,222 B2	4/2015	Bernick et al.	2003/0224057 A1	12/2003	Martin-Letellier et al.
9,012,434 B2	4/2015	Bernick et al.	2003/0224059 A1	12/2003	Lerner et al.
2001/0005728 A1	6/2001	Guittard et al.	2003/0225047 A1	12/2003	Caubel et al.
2001/0009673 A1	7/2001	Lipp et al.	2003/0225048 A1	12/2003	Caubel et al.
2001/0021816 A1	9/2001	Caillouette	2003/0225050 A1	12/2003	Grawe et al.
2001/0023261 A1	9/2001	Ryoo et al.	2003/0228686 A1	12/2003	Klausner et al.
2001/0027189 A1	10/2001	Bennink et al.	2003/0229057 A1	12/2003	Caubel et al.
2001/0029357 A1	10/2001	Bunt et al.	2003/0235596 A1	12/2003	Gao et al.
2001/0031747 A1	10/2001	deZiegler et al.	2003/0236236 A1	12/2003	Chen et al.
2001/0032125 A1	10/2001	Bhan et al.	2004/0009960 A1	1/2004	Heil et al.
2001/0034340 A1	10/2001	Pickar	2004/0022820 A1	2/2004	Anderson
2001/0053383 A1	12/2001	Miranda et al.	2004/0034001 A1	2/2004	Karara
2001/0056068 A1	12/2001	Chwalisz et al.	2004/0037881 A1	2/2004	Guittard et al.
2002/0012710 A1	1/2002	Lansky	2004/0039356 A1	2/2004	Maki et al.
2002/0026158 A1	2/2002	Rathbone et al.	2004/0043043 A1	3/2004	Schlyter et al.
2002/0028788 A1	3/2002	Bunt et al.	2004/0043943 A1	3/2004	Guittard et al.
2002/0035070 A1	3/2002	Gardlik et al.	2004/0044080 A1	3/2004	Place et al.
2002/0058648 A1	5/2002	Hammerly	2004/0048900 A1	3/2004	Flood
			2004/0052824 A1	3/2004	Abou Chacra-Vernet et al.
			2004/0073024 A1	4/2004	Metcalfe, III et al.
			2004/0077605 A1	4/2004	Salvati et al.
			2004/0077606 A1	4/2004	Salvati et al.



## US 9,301,920 B2

Page 6

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2004/0087548 A1	5/2004	Salvati et al.	2005/0250753 A1	11/2005	Fink et al.
2004/0087564 A1	5/2004	Wright et al.	2005/0256028 A1	11/2005	Yun et al.
2004/0089308 A1	5/2004	Welch	2005/0266078 A1	12/2005	Jorda et al.
2004/0092494 A9	5/2004	Dudley	2005/0266088 A1	12/2005	Hinrichs et al.
2004/0092583 A1	5/2004	Shanahan-Prendergast	2005/0271597 A1	12/2005	Keith
2004/0093261 A1	5/2004	Jain et al.	2005/0271598 A1	12/2005	Friedman et al.
2004/0097468 A1	5/2004	Wimalawansa	2005/0272685 A1	12/2005	Hung
2004/0101557 A1	5/2004	Gibson et al.	2005/0272712 A1	12/2005	Grubb et al.
2004/0106542 A1	6/2004	Deaver et al.	2006/0009428 A1	1/2006	Grubb et al.
2004/0110732 A1	6/2004	Masini-Eteve et al.	2006/0014728 A1	1/2006	Chwalisz et al.
2004/0131670 A1	7/2004	Gao	2006/0018937 A1	1/2006	Friedman et al.
2004/0138103 A1	7/2004	Patt	2006/0019978 A1	1/2006	Balog
2004/0142012 A1	7/2004	Bunt et al.	2006/0020002 A1	1/2006	Salvati et al.
2004/0146539 A1	7/2004	Gupta	2006/0030615 A1	2/2006	Fensome et al.
2004/0146894 A1	7/2004	Warrington et al.	2006/0034889 A1	2/2006	Jo et al.
2004/0161435 A1	8/2004	Gupta	2006/0034904 A1	2/2006	Weimann
2004/0176324 A1	9/2004	Salvati et al.	2006/0040904 A1	2/2006	Ahmed et al.
2004/0176336 A1	9/2004	Rodriguez	2006/0051391 A1	3/2006	Dvoskin et al.
2004/0185104 A1	9/2004	Piao et al.	2006/0052341 A1	3/2006	Cornish et al.
2004/0191207 A1	9/2004	Lipari et al.	2006/0069031 A1	3/2006	Loumaye
2004/0191276 A1	9/2004	Muni	2006/0078618 A1	4/2006	Constantinides et al.
2004/0198706 A1	10/2004	Carrara et al.	2006/0083778 A1	4/2006	Allison et al.
2004/0210280 A1	10/2004	Liedtke	2006/0084704 A1	4/2006	Shih et al.
2004/0213744 A1	10/2004	Lulla et al.	2006/0088580 A1	4/2006	Meconi et al.
2004/0219124 A1	11/2004	Gupta	2006/0089337 A1	4/2006	Casper et al.
2004/0225140 A1	11/2004	Fernandez et al.	2006/0093678 A1	5/2006	Chickering, III et al.
2004/0234606 A1	11/2004	Levine et al.	2006/0100180 A1	5/2006	Nubbemeyer et al.
2004/0241219 A1	12/2004	Hille et al.	2006/0106004 A1	5/2006	Brody et al.
2004/0243437 A1	12/2004	Grace et al.	2006/0110415 A1	5/2006	Gupta
2004/0253319 A1	12/2004	Netke et al.	2006/0111424 A1	5/2006	Salvati et al.
2004/0259817 A1	12/2004	Waldon et al.	2006/0121102 A1	6/2006	Chiang
2004/0266745 A1	12/2004	Schwanitz et al.	2006/0121626 A1	6/2006	Imrich
2005/0003003 A1	1/2005	Basu et al.	2006/0134188 A1	6/2006	Podhaisky et al.
2005/0004088 A1	1/2005	Hesch	2006/0135619 A1	6/2006	Kick et al.
2005/0009800 A1	1/2005	Thumbek et al.	2006/0165744 A1	7/2006	Jamil et al.
2005/0014729 A1	1/2005	Pulaski	2006/0193789 A1	8/2006	Tamarkin et al.
2005/0020550 A1	1/2005	Morris et al.	2006/0194775 A1	8/2006	Tofovic et al.
2005/0020552 A1	1/2005	Aschkenasy et al.	2006/0204557 A1	9/2006	Gupta et al.
2005/0021009 A1	1/2005	Massara et al.	2006/0233743 A1	10/2006	Kelly
2005/0025833 A1	2/2005	Aschkenasy et al.	2006/0233841 A1	10/2006	Brodbeck et al.
2005/0031651 A1	2/2005	Gervais et al.	2006/0235037 A1	10/2006	Purandare et al.
2005/0042173 A1	2/2005	Besse et al.	2006/0240111 A1	10/2006	Fernandez et al.
2005/0042268 A1	2/2005	Aschkenasy et al.	2006/0246122 A1	11/2006	Langguth et al.
2005/0048116 A1	3/2005	Straub et al.	2006/0247216 A1	11/2006	Haj-Yehia
2005/0054991 A1	3/2005	Tobyn et al.	2006/0247221 A1	11/2006	Coelingh Bennink et al.
2005/0079138 A1	4/2005	Chickering, III et al.	2006/0251581 A1	11/2006	McIntyre et al.
2005/0085453 A1	4/2005	Govindarajan	2006/0252049 A1	11/2006	Shuler et al.
2005/0101579 A1	5/2005	Shippen	2006/0257472 A1	11/2006	Nielsen
2005/0113350 A1	5/2005	Duesterberg et al.	2006/0275218 A1	12/2006	Tamarkin et al.
2005/0118244 A1	6/2005	Theobald et al.	2006/0275360 A1	12/2006	Ahmed et al.
2005/0118272 A1	6/2005	Besse et al.	2006/0276414 A1	12/2006	Coelingh Bennink et al.
2005/0129756 A1	6/2005	Podhaisky et al.	2006/0280771 A1	12/2006	Groenewegen et al.
2005/0152956 A1	7/2005	Dudley	2006/0280797 A1	12/2006	Shoichet et al.
2005/0153946 A1	7/2005	Hirsh et al.	2006/0280800 A1	12/2006	Nagi et al.
2005/0164977 A1	7/2005	Coelingh Bennink	2006/0292223 A1	12/2006	Woolfson et al.
2005/0182105 A1	8/2005	Nirschl et al.	2007/0004693 A1	1/2007	Woolfson et al.
2005/0186141 A1	8/2005	Gonda et al.	2007/0004694 A1	1/2007	Woolfson et al.
2005/0187267 A1	8/2005	Hamann et al.	2007/0009559 A1	1/2007	Li et al.
2005/0192253 A1	9/2005	Salvati et al.	2007/0009594 A1	1/2007	Grubb et al.
2005/0192310 A1	9/2005	Gavai et al.	2007/0010550 A1	1/2007	McKenzie
2005/0196434 A1	9/2005	Brierre	2007/0014839 A1	1/2007	Bracht
2005/0207990 A1	9/2005	Funke et al.	2007/0015698 A1	1/2007	Kleinman et al.
2005/0214384 A1	9/2005	Juturu et al.	2007/0021360 A1	1/2007	Nyce et al.
2005/0220825 A1	10/2005	Funke et al.	2007/0027201 A1	2/2007	McComas et al.
2005/0220900 A1	10/2005	Popp et al.	2007/0031491 A1	2/2007	Levine et al.
2005/0222106 A1	10/2005	Bracht	2007/0037780 A1	2/2007	Ebert et al.
2005/0228692 A1	10/2005	Hodgdon	2007/0037782 A1	2/2007	Hibino et al.
2005/0228718 A1	10/2005	Austin	2007/0042038 A1	2/2007	Besse
2005/0239747 A1	10/2005	Yang et al.	2007/0060589 A1	3/2007	Purandare et al.
2005/0239758 A1	10/2005	Roby	2007/0066628 A1	3/2007	Zhang et al.
2005/0244360 A1	11/2005	Billoni	2007/0066637 A1	3/2007	Zhang et al.
2005/0244522 A1	11/2005	Carrara et al.	2007/0066675 A1	3/2007	Zhang et al.
2005/0245902 A1	11/2005	Cornish et al.	2007/0078091 A1	4/2007	Hubler et al.
2005/0250746 A1	11/2005	Iammatteo	2007/0088029 A1	4/2007	Balog et al.
2005/0250750 A1	11/2005	Cummings et al.	2007/0093548 A1	4/2007	Diffendal et al.
			2007/0116729 A1	5/2007	Palepu
			2007/0116829 A1	5/2007	Prakash et al.
			2007/0128263 A1	6/2007	Gargiulo et al.
			2007/0154533 A1	7/2007	Dudley



## US 9,301,920 B2

Page 7

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2007/0167418 A1	7/2007	Ferguson	2009/0022683 A1	1/2009	Song et al.
2007/0178166 A1	8/2007	Bernstein et al.	2009/0047357 A1	2/2009	Tomohira et al.
2007/0184558 A1	8/2007	Roth et al.	2009/0053294 A1	2/2009	Prendergast
2007/0185068 A1	8/2007	Ferguson et al.	2009/0060982 A1	3/2009	Ron et al.
2007/0190022 A1	8/2007	Bacopoulos et al.	2009/0060997 A1	3/2009	Seitz et al.
2007/0191319 A1	8/2007	Ke et al.	2009/0068118 A1	3/2009	Eini et al.
2007/0196415 A1	8/2007	Chen et al.	2009/0081206 A1	3/2009	Leibovitz
2007/0196433 A1	8/2007	Ron et al.	2009/0081278 A1	3/2009	De Graaff et al.
2007/0207225 A1	9/2007	Squadrito	2009/0081303 A1	3/2009	Savoit et al.
2007/0225281 A1	9/2007	Zhang et al.	2009/0092656 A1	4/2009	Klamerus et al.
2007/0232574 A1	10/2007	Galey et al.	2009/0093440 A1	4/2009	Murad
2007/0238713 A1	10/2007	Gast et al.	2009/0098069 A1	4/2009	Vacca
2007/0243229 A1	10/2007	Smith et al.	2009/0099106 A1	4/2009	Phiasivongsa et al.
2007/0248658 A1	10/2007	Zurdo Schroeder et al.	2009/0099149 A1	4/2009	Liu et al.
2007/0254858 A1	11/2007	Cronk	2009/0130029 A1	5/2009	Tamarkin et al.
2007/0255197 A1	11/2007	Humberstone et al.	2009/0131385 A1	5/2009	Voskuhl
2007/0264309 A1	11/2007	Chollet et al.	2009/0137478 A1	5/2009	Bernstein et al.
2007/0264345 A1	11/2007	Eros et al.	2009/0137538 A1	5/2009	Klamerus et al.
2007/0264349 A1	11/2007	Lee et al.	2009/0143344 A1	6/2009	Chang
2007/0286819 A1	12/2007	DeVries et al.	2009/0164341 A1	6/2009	Sunvold et al.
2007/0287688 A1	12/2007	Chan et al.	2009/0175799 A1	7/2009	Tamarkin et al.
2007/0287789 A1	12/2007	Jones et al.	2009/0181088 A1	7/2009	Song et al.
2007/0292359 A1	12/2007	Friedman et al.	2009/0186081 A1	7/2009	Holm et al.
2007/0292387 A1	12/2007	Jon et al.	2009/0197843 A1	8/2009	Notelovitz et al.
2007/0292461 A1	12/2007	Tamarkin et al.	2009/0203658 A1	8/2009	Marx et al.
2007/0292493 A1	12/2007	Brierre	2009/0214474 A1	8/2009	Jennings
2007/0298089 A1	12/2007	Saeki et al.	2009/0227025 A1	9/2009	Nichols et al.
2008/0026035 A1	1/2008	Chollet et al.	2009/0227550 A1	9/2009	Mattern
2008/0026040 A1	1/2008	Farr et al.	2009/0232897 A1	9/2009	Sahoo et al.
2008/0026062 A1	1/2008	Farr et al.	2009/0258096 A1	10/2009	Cohen
2008/0038219 A1	2/2008	Mosbaugh et al.	2009/0264395 A1	10/2009	Creasy
2008/0038350 A1	2/2008	Gerecke et al.	2009/0269403 A1	10/2009	Shaked et al.
2008/0039405 A1	2/2008	Langley et al.	2009/0285772 A1	11/2009	Phiasivongsa et al.
2008/0050317 A1	2/2008	Tamarkin et al.	2009/0285869 A1	11/2009	Trimble
2008/0051351 A1	2/2008	Ghisalberti	2009/0318558 A1	12/2009	Kim et al.
2008/0063607 A1	3/2008	Tamarkin et al.	2009/0324714 A1	12/2009	Liu et al.
2008/0069779 A1	3/2008	Tamarkin et al.	2009/0325916 A1	12/2009	Zhang et al.
2008/0069791 A1	3/2008	Beissert	2010/0008985 A1	1/2010	Pellikaan et al.
2008/0085877 A1	4/2008	Bortz	2010/0028360 A1	2/2010	Atwood
2008/0095831 A1	4/2008	McGraw	2010/0034838 A1	2/2010	Staniforth et al.
2008/0095838 A1	4/2008	Abou Chacra-Vernet	2010/0034880 A1	2/2010	Sintov et al.
2008/0113953 A1	5/2008	De Vries et al.	2010/0040671 A1	2/2010	Ahmed et al.
2008/0114050 A1	5/2008	Fensome et al.	2010/0048523 A1	2/2010	Bachman et al.
2008/0119537 A1	5/2008	Zhang et al.	2010/0055138 A1	3/2010	Margulies et al.
2008/0125402 A1	5/2008	Dilberti	2010/0074959 A1	3/2010	Hansom et al.
2008/0138379 A1	6/2008	Jennings-Spring	2010/0086501 A1	4/2010	Chang et al.
2008/0138390 A1	6/2008	Hsu et al.	2010/0086599 A1	4/2010	Huempel et al.
2008/0139392 A1	6/2008	Acosta Zara et al.	2010/0092568 A1	4/2010	Lerner et al.
2008/0145423 A1	6/2008	Khan et al.	2010/0105071 A1	4/2010	Laufer et al.
2008/0153789 A1	6/2008	Dmowski et al.	2010/0119585 A1	5/2010	Hille et al.
2008/0175814 A1	7/2008	Phiasivongsa et al.	2010/0129320 A1	5/2010	Phiasivongsa et al.
2008/0175905 A1	7/2008	Liu et al.	2010/0136105 A1	6/2010	Chen et al.
2008/0175908 A1	7/2008	Liu et al.	2010/0137265 A1	6/2010	Leonard
2008/0188829 A1	8/2008	Creasy	2010/0137271 A1	6/2010	Chen et al.
2008/0206156 A1	8/2008	Cronk	2010/0143420 A1	6/2010	Shenoy et al.
2008/0206159 A1	8/2008	Tamarkin et al.	2010/0143481 A1	6/2010	Shenoy et al.
2008/0206161 A1	8/2008	Tamarkin et al.	2010/0150993 A1	6/2010	Theobald et al.
2008/0214512 A1	9/2008	Seitz et al.	2010/0152144 A1	6/2010	Hermesmyer
2008/0220069 A1	9/2008	Allison	2010/0168228 A1	7/2010	Bose et al.
2008/0226698 A1	9/2008	Tang et al.	2010/0183723 A1	7/2010	Laurent-Applegate et al.
2008/0227763 A1	9/2008	Lanquetin et al.	2010/0184736 A1	7/2010	Coelingh Bennink et al.
2008/0234199 A1	9/2008	Katamreddy	2010/0190758 A1	7/2010	Fausser et al.
2008/0234240 A1	9/2008	Duesterberg et al.	2010/0204326 A1	8/2010	D Souza
2008/0255078 A1	10/2008	Katamreddy	2010/0210994 A1	8/2010	Zarif
2008/0255089 A1	10/2008	Katamreddy	2010/0221195 A1	9/2010	Tamarkin et al.
2008/0261931 A1	10/2008	Hedner et al.	2010/0227797 A1	9/2010	Axelson et al.
2008/0299220 A1	12/2008	Tamarkin et al.	2010/0240626 A1	9/2010	Kulkarni et al.
2008/0306036 A1	12/2008	Katamreddy	2010/0247482 A1	9/2010	Cui et al.
2008/0312197 A1	12/2008	Rodriguez	2010/0247632 A1	9/2010	Dong et al.
2008/0312198 A1	12/2008	Rodriguez	2010/0247635 A1	9/2010	Rosenberg et al.
2008/0319078 A1	12/2008	Katamreddy	2010/0255085 A1	10/2010	Liu et al.
2009/0004246 A1	1/2009	Woolfson et al.	2010/0273730 A1	10/2010	Hsu et al.
2009/0010968 A1	1/2009	Allart et al.	2010/0278759 A1	11/2010	Murad
2009/0011041 A1	1/2009	Musaeva et al.	2010/0279988 A1	11/2010	Setiawan et al.
2009/0017120 A1	1/2009	Trimble et al.	2010/0291191 A1	11/2010	Shoichet et al.
			2010/0292199 A1	11/2010	Leverd et al.
			2010/0303825 A9	12/2010	Sirbasku
			2010/0312137 A1	12/2010	Gilmour et al.
			2010/0316724 A1	12/2010	Whitfield et al.

## US 9,301,920 B2

Page 8

(56)	<b>References Cited</b>					
	U.S. PATENT DOCUMENTS					
2010/0322884	A1	12/2010	Dipietro et al.	2012/0129773	A1	5/2012 Geier et al.
2010/0330168	A1	12/2010	Gicquel et al.	2012/0129819	A1	5/2012 Vancaillie et al.
2011/0028439	A1	2/2011	Witt-Enderby et al.	2012/0136013	A1	5/2012 Li et al.
2011/0039814	A1	2/2011	Huatan et al.	2012/0142645	A1	6/2012 Marx
2011/0053845	A1	3/2011	Levine et al.	2012/0148670	A1	6/2012 Kim et al.
2011/0066473	A1	3/2011	Bernick et al.	2012/0149748	A1	6/2012 Shanler et al.
2011/0076775	A1	3/2011	Stewart et al.	2012/0172343	A1	7/2012 Lindenthal et al.
2011/0076776	A1	3/2011	Stewart et al.	2012/0184515	A1	7/2012 Klar et al.
2011/0086825	A1	4/2011	Chatroux	2012/0231052	A1	9/2012 Sitruk Ware et al.
2011/0087192	A1	4/2011	Uhland et al.	2012/0232011	A1	9/2012 Kneissel et al.
2011/0091555	A1	4/2011	De Luigi Bruschi et al.	2012/0232042	A1	9/2012 Klar et al.
2011/0098258	A1	4/2011	Masini Eteve et al.	2012/0263679	A1	10/2012 Marlow et al.
2011/0098631	A1	4/2011	McIntyre et al.	2012/0269721	A1	10/2012 Weng et al.
2011/0104268	A1	5/2011	Pachot et al.	2012/0269878	A2	10/2012 Cantor et al.
2011/0104289	A1	5/2011	Savoir Vilboeuf et al.	2012/0277249	A1	11/2012 Andersson et al.
2011/0130372	A1	6/2011	Agostinacchio et al.	2012/0277727	A1	11/2012 Doshi et al.
2011/0135719	A1	6/2011	Besins et al.	2012/0283671	A1	11/2012 Shibata et al.
2011/0142945	A1	6/2011	Chen et al.	2012/0295911	A1	11/2012 Mannion et al.
2011/0152840	A1	6/2011	Lee et al.	2012/0301517	A1	11/2012 Zhang et al.
2011/0158920	A1	6/2011	Morley et al.	2012/0301538	A1	11/2012 Gordon Beresford et al.
2011/0171140	A1	7/2011	Illum et al.	2012/0302535	A1	11/2012 Caufriez et al.
2011/0182997	A1	7/2011	Lewis et al.	2012/0316130	A1	12/2012 Hendrix
2011/0190201	A1	8/2011	Hyde et al.	2012/0316496	A1	12/2012 Hoffmann et al.
2011/0195031	A1	8/2011	Du	2012/0321579	A1	12/2012 Edelson et al.
2011/0195114	A1	8/2011	Carrara et al.	2012/0322779	A9	12/2012 Voskuhl
2011/0195944	A1	8/2011	Mura et al.	2012/0328549	A1	12/2012 Edelson et al.
2011/0217341	A1	9/2011	Sah	2012/0329738	A1	12/2012 Liu
2011/0238003	A1	9/2011	Bruno Raimondi et al.	2013/0004619	A1	1/2013 Chow et al.
2011/0244043	A1	10/2011	Xu et al.	2013/0011342	A1	1/2013 Tamarkin et al.
2011/0250256	A1	10/2011	Hyun Oh et al.	2013/0017239	A1	1/2013 Viladot Petit et al.
2011/0250259	A1	10/2011	Buckman	2013/0022674	A1	1/2013 Dudley et al.
2011/0250274	A1	10/2011	Shaked et al.	2013/0023505	A1	1/2013 Garfield et al.
2011/0256092	A1	10/2011	Phiasivongsa et al.	2013/0023823	A1	1/2013 Simpson et al.
2011/0262373	A1	10/2011	Umbert Millet	2013/0028850	A1	1/2013 Tamarkin et al.
2011/0262494	A1	10/2011	Achleitner et al.	2013/0029947	A1	1/2013 Nachaegari et al.
2011/0268665	A1	11/2011	Tamarkin et al.	2013/0029957	A1	1/2013 Giliyar et al.
2011/0275584	A1	11/2011	Wilckens et al.	2013/0045266	A1	2/2013 Choi et al.
2011/0281832	A1	11/2011	Li et al.	2013/0045953	A1	2/2013 Sitruk Ware et al.
2011/0287094	A1	11/2011	Penhasi et al.	2013/0059795	A1	3/2013 Lo et al.
2011/0293720	A1	12/2011	General et al.	2013/0064897	A1	3/2013 Binay
2011/0294738	A1	12/2011	Ren et al.	2013/0072466	A1	3/2013 Choi et al.
2011/0300167	A1	12/2011	Mcmurry et al.	2013/0084257	A1	4/2013 Ishida et al.
2011/0301087	A1	12/2011	Mcbride et al.	2013/0085123	A1	4/2013 Li et al.
2011/0306579	A1	12/2011	Stein	2013/0089574	A1	4/2013 Schmidt Gollwitzer et al.
2011/0311592	A1	12/2011	Birbara	2013/0090318	A1	4/2013 Ulmann et al.
2011/0312927	A1	12/2011	Nachaegari et al.	2013/0102781	A1	4/2013 Beville et al.
2011/0312928	A1	12/2011	Nachaegari et al.	2013/0108551	A1	5/2013 Langereis et al.
2011/0318405	A1	12/2011	Erwin	2013/0116215	A1	5/2013 Coma et al.
2011/0318431	A1	12/2011	Gulati	2013/0116222	A1	5/2013 Arnold et al.
2012/0009276	A1	1/2012	De Groote	2013/0122051	A1	5/2013 Abidi et al.
2012/0015350	A1	1/2012	Nabatiyan et al.	2013/0123175	A1	5/2013 Hill et al.
2012/0021041	A1	1/2012	Rossi et al.	2013/0123220	A1	5/2013 Queiroz
2012/0028888	A1	2/2012	Janz et al.	2013/0123351	A1	5/2013 Dewitt
2012/0028910	A1	2/2012	Combal et al.	2013/0129818	A1	5/2013 Bernick et al.
2012/0028936	A1	2/2012	Gloger et al.	2013/0131027	A1	5/2013 Pakkalin et al.
2012/0045532	A1	2/2012	Cohen	2013/0131028	A1	5/2013 Snyder et al.
2012/0046264	A1	2/2012	Simes et al.	2013/0131029	A1	5/2013 Bakker et al.
2012/0046518	A1	2/2012	Yoakum et al.	2013/0149314	A1	6/2013 Bullerdiek et al.
2012/0052077	A1	3/2012	Truitt, III et al.	2013/0164225	A1	6/2013 Tamarkin et al.
2012/0058171	A1	3/2012	De Graaff et al.	2013/0164346	A1	6/2013 Lee et al.
2012/0058962	A1	3/2012	Cumming et al.	2013/0165744	A1	6/2013 Carson et al.
2012/0058979	A1	3/2012	Keith et al.	2013/0178452	A1	7/2013 King
2012/0064135	A1	3/2012	Levin et al.	2013/0183254	A1	7/2013 Zhou et al.
2012/0065179	A1	3/2012	Andersson	2013/0183325	A1	7/2013 Bottoni et al.
2012/0065221	A1	3/2012	Babul	2013/0189193	A1	7/2013 Tamarkin et al.
2012/0087872	A1	4/2012	Tamarkin et al.	2013/0189196	A1	7/2013 Tamarkin et al.
2012/0101073	A1	4/2012	Mannion et al.	2013/0189230	A1	7/2013 Shoichet et al.
2012/0121517	A1	5/2012	Song et al.	2013/0189368	A1	7/2013 Mosqueira et al.
2012/0121692	A1	5/2012	Xu et al.	2013/0210709	A1	8/2013 Mcmurry et al.
2012/0122829	A1	5/2012	Taravella et al.	2013/0216550	A1	8/2013 Penninger et al.
2012/0128625	A1	5/2012	Shalwitz et al.	2013/0216596	A1	8/2013 Viladot Petit et al.
2012/0128654	A1	5/2012	Terpstra et al.	2013/0224177	A1	8/2013 Kim et al.
2012/0128683	A1	5/2012	Shantha	2013/0224257	A1	8/2013 Sah et al.
2012/0128733	A1	5/2012	Perrin et al.	2013/0224268	A1	8/2013 Alam et al.
2012/0128777	A1	5/2012	Keck et al.	2013/0224300	A1	8/2013 Maggio
				2013/0225412	A1	8/2013 Sardari Lodriche et al.
				2013/0225542	A1	8/2013 Poeigh et al.
				2013/0226113	A1	8/2013 Schumacher et al.
				2013/0243696	A1	9/2013 Wang et al.

## US 9,301,920 B2

Page 9

(56)	<b>References Cited</b>			WO	9422426	A1	3/1994
	U.S. PATENT DOCUMENTS			WO	9530409	A1	11/1995
				WO	9609826	A2	4/1996
				WO	9619975		7/1996
2013/0245253	A1	9/2013	Marx et al.	WO	9630000	A1	10/1996
2013/0245570	A1	9/2013	Jackson	WO	9705491		2/1997
2013/0261096	A1	10/2013	Merian et al.	WO	9743989	A1	11/1997
2013/0266645	A1	10/2013	Becker et al.	WO	9810293	A1	3/1998
2013/0267485	A1	10/2013	Da Silva Maia Filho	WO	9832465	A1	7/1998
2013/0273167	A1	10/2013	Lee et al.	WO	9851280	A1	11/1998
2013/0274211	A1	10/2013	Burman et al.	WO	9939700	A1	2/1999
2013/0280213	A1	10/2013	Voskuhl	WO	9932072	A1	7/1999
2013/0316374	A1	11/2013	Penninger et al.	WO	9942109	A1	8/1999
2013/0317065	A1	11/2013	Tatani et al.	WO	9943304		9/1999
2013/0317315	A1	11/2013	Lu et al.	WO	9948477	A1	9/1999
2013/0324565	A1	12/2013	Li et al.	WO	9953910	A2	10/1999
2013/0331363	A1	12/2013	Li et al.	WO	9963974	A2	12/1999
2013/0338122	A1	12/2013	Bernick et al.	WO	0001351	A1	1/2000
2013/0338124	A1	12/2013	Li et al.	WO	0006175	A1	2/2000
2013/0345187	A1	12/2013	Rodriguez Oquendo	WO	0038659	A1	7/2000
2014/0018335	A1	1/2014	Tatani et al.	WO	0045795	A2	8/2000
2014/0024590	A1	1/2014	Weidhaas et al.	WO	0050007	A1	8/2000
2014/0031289	A1	1/2014	Song et al.	WO	0059577	A1	10/2000
2014/0031323	A1	1/2014	Perez	WO	0076522	A1	12/2000
2014/0066416	A1	3/2014	Leunis et al.	WO	0137808	A1	5/2001
2014/0072531	A1	3/2014	Kim et al.	WO	0154699	A1	8/2001
2014/0079686	A1	3/2014	Barman et al.	WO	0160325	A1	8/2001
2014/0088051	A1	3/2014	Bernick et al.	WO	0207700	A2	1/2002
2014/0088058	A1	3/2014	Maurizio	WO	0211768	A1	2/2002
2014/0088059	A1	3/2014	Perumal et al.	WO	0222132	A2	3/2002
2014/0094426	A1	4/2014	Drummond et al.	WO	0240008	A2	5/2002
2014/0094440	A1	4/2014	Bernick et al.	WO	0241878		5/2002
2014/0094441	A1	4/2014	Bernick et al.	WO	02053131	A1	7/2002
2014/0099362	A1	4/2014	Bernick et al.	WO	02078602	A2	10/2002
2014/0100159	A1	4/2014	Conrad	WO	02078604	A2	10/2002
2014/0100204	A1	4/2014	Bernick et al.	WO	03028667		4/2003
2014/0100205	A1	4/2014	Bernick et al.	WO	03041718	A1	5/2003
2014/0100206	A1	4/2014	Bernick et al.	WO	03041741	A1	5/2003
2014/0113889	A1	4/2014	Connor et al.	WO	03068186	A1	8/2003
2014/0127185	A1	5/2014	Stein et al.	WO	03077923	A1	9/2003
2014/0127280	A1	5/2014	Duesterberg et al.	WO	03082254	A1	10/2003
2014/0127308	A1	5/2014	Opara et al.	WO	03092588	A2	11/2003
2014/0128798	A1	5/2014	Janson et al.	WO	2004014432		2/2004
2014/0148491	A1	5/2014	Valia et al.	WO	2004017983	A1	3/2004
2014/0186332	A1	7/2014	Ezrin et al.	WO	2005027911	A1	3/2004
2014/0187487	A1	7/2014	Shoichet et al.	WO	2004032897	A2	4/2004
2014/0193523	A1	7/2014	Henry	WO	2004052336	A2	6/2004
2014/0194396	A1	7/2014	Li et al.	WO	2005120517	A1	6/2004
2014/0206616	A1	7/2014	Ko et al.	WO	2004054540	A2	7/2004
2014/0213565	A1	7/2014	Bernick et al.	WO	2004080413	A2	9/2004
2014/0329783	A1	11/2014	Bernick et al.	WO	2005030175	A1	4/2005
2014/0371182	A1	12/2014	Bernick et al.	WO	2005081825		9/2005
2014/0371183	A1	12/2014	Bernick et al.	WO	2005087194	A1	9/2005
2014/0371184	A1	12/2014	Bernick et al.	WO	2005087199	A2	9/2005
2014/0371185	A1	12/2014	Bernick et al.	WO	2005105059	A1	11/2005
2015/0031654	A1	1/2015	Amadio	WO	2005115335	A1	12/2005
2015/0045335	A1	2/2015	Bernick et al.	WO	2005120470	A1	12/2005
2015/0133421	A1	5/2015	Bernick et al.	WO	2006013369	A2	2/2006
				WO	2006034090	A1	3/2006
				WO	2006036899	A2	4/2006
				WO	2006053172	A2	5/2006
				WO	2006105615	A1	10/2006
				WO	2006113505	A2	10/2006
EP	0275716		7/1988	WO	2006138686	A1	12/2006
EP	0622075	A1	11/1994	WO	2006138735	A2	12/2006
EP	0785211	A1	1/1996	WO	2007045027	A1	4/2007
EP	0785212	A1	1/1996	WO	2007103294	A2	9/2007
EP	0811381	A1	6/1997	WO	2007120868		10/2007
EP	1094781	B1	7/2008	WO	2007123790	A1	11/2007
EP	2191833	A1	6/2010	WO	2007124250	A2	11/2007
GB	452238	A	8/1936	WO	2007144151	A1	12/2007
GB	720561		12/1954	WO	2008049516	A3	5/2008
GB	848881	A1	9/1960	WO	2008152444	A2	12/2008
GB	874368		8/1961	WO	2009002542	A1	12/2008
GB	1589946		5/1981	WO	2009036311	A1	3/2009
IN	216026		3/2008	WO	2009040818		4/2009
IN	2005KO00053		9/2009	WO	2009069006	A2	6/2009
IN	244217		11/2010	WO	2009098072	A2	8/2009
WO	9011064	A1	10/1990	WO	2009133352	A2	11/2009
WO	9317686	A1	9/1993	WO			

## US 9,301,920 B2

Page 10

(56)

## References Cited

## FOREIGN PATENT DOCUMENTS

WO	2010033188	A2	3/2010
WO	2010146872		12/2010
WO	2011000210	A1	1/2011
WO	2011073995	A2	6/2011
WO	2011120084	A1	10/2011
WO	2011128336	A1	10/2011
WO	2012009778	A2	1/2012
WO	2012024361	A1	2/2012
WO	2012055814	A1	5/2012
WO	2012055840	A1	5/2012
WO	2012065740		5/2012
WO	2012098090	A1	7/2012
WO	2012116277	A1	8/2012
WO	2012118563	A2	9/2012
WO	2012120365	A1	9/2012
WO	2012127501	A2	9/2012
WO	2012156561	A1	11/2012
WO	2012156822	A1	11/2012
WO	2012158483	A2	11/2012
WO	2012166909	A1	12/2012
WO	2012170578	A1	12/2012
WO	2013011501	A1	1/2013
WO	2013025449	A1	2/2013
WO	2013028639	A1	2/2013
WO	2013035101	A1	3/2013
WO	2013044067	A1	3/2013
WO	2013045404	A2	4/2013
WO	2013059285	A1	4/2013
WO	2013063279	A1	5/2013
WO	2013064620	A1	5/2013
WO	2013071281	A1	5/2013
WO	2013088254		6/2013
WO	2013102665	A1	7/2013
WO	2013106437	A1	7/2013
WO	2013113690		8/2013
WO	2013124415	A1	8/2013
WO	2013127727	A1	9/2013
WO	2013127728	A1	9/2013
WO	2013144356	A1	10/2013
WO	2013149258	A2	10/2013
WO	2013158454	A2	10/2013
WO	2013170052	A1	11/2013
WO	2013178587	A1	12/2013
WO	2013181449	A1	12/2013
WO	2013192248	A1	12/2013
WO	2013192249	A1	12/2013
WO	2013192250	A1	12/2013
WO	2013192251	A1	12/2013
WO	2014001904	A1	1/2014
WO	2014004424	A1	1/2014
WO	2014009434	A1	1/2014
WO	2014018569	A1	1/2014
WO	2014018570	A1	1/2014
WO	2014018571	A2	1/2014
WO	2014018856	A1	1/2014
WO	2014018932	A2	1/2014
WO	2014031958	A1	2/2014
WO	2014041120	A1	3/2014
WO	2014052792	A1	4/2014
WO	2014056897	A1	4/2014
WO	2014066442	A2	5/2014
WO	2014074846	A1	5/2014
WO	2014076231	A1	5/2014
WO	2014076569	A2	5/2014
WO	2014081598	A1	5/2014
WO	2014086739	A1	6/2014
WO	2014093114	A1	6/2014
WO	2014104784	A1	7/2014

## OTHER PUBLICATIONS

James Simon et al., "Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet," *Obstetrics & Gynecology* 2008;112(5):1053-1060.  
USPTO; Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.

USPTO; Notice of Allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002.

USPTO; Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545.

USPTO; Restriction/ Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562.

USPTO; Restriction/ Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623.

US 6,214,374, Apr. 10, 2001, Schmirler et al. (withdrawn).

International Search Report and Written Opinion for related International Application No. PCT/US13/023309 mailed Apr. 9, 2013.

International Search report for corresponding International Application No. PCT/US12/66406, mailed Jan. 24, 2013.

Azure Pharma, Inc., "ELESTRIN™—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages (Aug. 2009).

Panchagnula et al., "Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol as a cosolvent: in-vitro, ex-vivo and in-vivo rat studies," *J Pharm Pharmacol.* 43(9):609-614 (Sep. 1991). Abstract Only.

Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," *J. Kor. Pharm. Sci.*, 35(3):173-177, (2005).

NuGen, "What is NuGen HP Hair Growth System?" <http://www.skinnergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, (undated), 3 pages.

NuGest 900™, <http://www.thehormoneshop.net/nugest900.htm>, (undated), 4 pages.

Tahitian Noni, "Body Balance Cream," [http://products.tni.com/dominican\\_republic/sa\\_spanish/nonistore/product/3438/3416/](http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/), (undated), 1 page.

Knuth et al., "Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations," *Advanced Drug Delivery Reviews*, 11(1-2):137-167 (Jul.-Aug. 1993). Abstract Only.  
Lucy et al., "Gonadotropin-releasing hormone at estrus: luteinizing hormone, estradiol, and progesterone during the periestrual and postinsemination periods in dairy cattle," *Biol Reprod.* 35(2):300-311 (1986). Abstract Only.

Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," *International Journal of Pharmaceutics*, 147(2):165-171 (Feb. 1997). Abstract Only.

Diramio, "Polyethylene Glycol Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," *The University of Georgia-Masters of Science Thesis*, 131 pages. (2004). [http://athenaeum.libs.uga.edu/bitstream/handle/10724/7820/diramio\\_jackie\\_a\\_200412\\_ms.pdf?sequence=1](http://athenaeum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1).

Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," *Drug Development and Industrial Pharmacy*, 35(5):525-547 (May 2009). Abstract Only.

Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," *Pharmaceutical Research*, 21(2):201-230 (Feb. 2004). Abstract Only.

Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," *Critical Reviews in Toxicology*, 30(3):307-345 (2000). Abstract Only.

Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," *Skin Pharmacol Physiol*, 19:106-121 (2006). [http://www.nanobiotech.iqm.unicamp.br/download/Trommer\\_skin%20penetration-2006rev.pdf](http://www.nanobiotech.iqm.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf).

Committee of Obstetric Practice, Committee Opinion—No. 522, *Obstetrics & Gynecology*, 119(4):879-882 (Apr. 2012).

Salole, "The physiochemical properties of oestradiol," *Journal of Pharmaceutical & Biomedical Analysis*, 5(7):635-648 (1987).

Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.

ACOG, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists, ACOG, No. 141, vol. 123, No. 1, Jan. 2014, Obstetrics & Gynecology.

Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.



## US 9,301,920 B2

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(56)

## References Cited

## OTHER PUBLICATIONS

- Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via CocrySTALLIZATION, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, Steroids, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M, Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , Vibrational Spectroscopy 8, Elsevier, pp. 263, 1995.
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, Bollettino Chimico Farmaceutico, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, Acta Pharm. Jugosl., vol. 40 pp. 71-94, 1990.
- Brandstatter-Kuhnert, M, Zur mikroskopischen Identitätsprüfung und zur Polymorphie der Sexualhormone, Acta, vol. 6, pp. 847-853, 1959, Univ. Innsbruck.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Buray, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, Am J Obstet Gynecol, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moléculaire de l'Oestradiol Hemihydrate, Acta Cryst., B28 pp. 560, 1972, Bis(dimethyl-o-thiophenylarsine)palladium(II).
- Busetta, Par Bernard, Structure Cristalline et Moléculaire du Complexe Oestradiol-Propanol, Acta Cryst., B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.
- Campsteyn, Par H, et al., Structure Cristalline et Moléculaire de la Progesterone C21H30O2, Acta Cryst., B28 pp. 3032-3042, 1972.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, Revista Mexicana de Fisica, 50, Suplemento 1 pp. 1-3, 2004.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Commodari, Fernando, Comparison of 17B-estradiol structures from x-ray diffraction and solution NMR, Magn. Reson. Chem., vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, The Lancet, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Dideberg, O, et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , J. Appl. Cryst. vol. 4 pp. 80, 1971.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , Inter. Journal of Pharmaceutics, Elsevier, vol. 363, pp. 40-49, 2009.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, J. Am. Chem. Soc., vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , J. Thermal Anal., vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, SciFinder, Pharmaceutica Acta Helvetica, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, Pharmaceutical Research, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, Journal of General Internal Medicine, vol. 22, pp. 1030-1034, 2007.
- Giron, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, Thermochimica Acta, vol. 248 pp. 1-59, 1995, Elsevier.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, J. Pharmaceutical & Biomedical Anal., vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, Acta Cryst., vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, Pharm Res, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, Jour. of Mag. Resonance, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, Mol. Pharmacology, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, Pharmaceutical Development and Tech., vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Idder, Salima, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johnson, William S, et al., Racemic Progesterone, Tetrahedron Letters No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, Drug Dev. & Indus. Pharm., vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Korkmaz, Filiz, Biophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, Journal of Pharmaceutical and Biomedical Analysis, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminiewski, R, et al., EPR Study of the Stable Radical in a  $\gamma$ -Irradiated Single Crystal of Progesterone, Jour. of Mag. Resonance, vol. 46 pp. 300-305, 1982, Academic Press.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.

## US 9,301,920 B2

Page 12

(56)

## References Cited

## OTHER PUBLICATIONS

- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone, SciFinder Scholar Search, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Struhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M, et al., The light sensitivity of corticosteroids in crystalline form, *Pharmaceutica acta Helvetiae*, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S, et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: an . . . , *Intl. J. of Pharmaceut.*, vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, *AAPS PhamSciTech*, vol. 11, No. 3, Sep. 2010.
- USP Monographs: Progesterone, USP29, [www.pharmacopeia.cn/v29240/usp29nf24s0\\_m69870.html](http://www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html), search done: Feb. 25, 2014.
- Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . *Fertility and Sterility*, vol. 75(6) pp. 1065, Jun. 2001.
- Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, *Thermochimica Acta* 485, Elsevier, pp. 57, 2009.
- Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, *J. of Pharmaceutical Sciences*, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, *Handbook of Aqueous Solubility Data*, Solutions, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
- Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, *Journal of Steroid Biochem & Mol Biology*, vol. 86 pp. 477-486, 2003.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, *Jour. of Mol. Structure, Theochem*, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, *Jour. of Mol. Structure, Theochem* vol. 425, pp. 171-179, 1998, Elsevier.
- Kuhnert-Brandstaetter, M & Kofler, A, Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II. vol. 1 pp. 127-139, 1968, *Mikrochimica Acta*.
- Kuhnert-Brandstaetter, M & Linder, R, Zur Hydratbildung bei Steroidhormonen, *Sci. Pharm.*, vol. 41(2) pp. 109-116, 1973.
- Kuhnert-Brandstaetter, M, Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , *Drug Development and Industrial Pharmacy*, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steroids, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G., et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , *Maturitas*, *The European Menopaus Journal*, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroidal conformation of 17a- and 17B-estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17b and Progesterone Concentrations in Uterine Lymph and Systematic Blood . . . , *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, *Catalent Pharma Solutions*, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MONO1500003758.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B- Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*, 35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://lxsrv7.oru.edu/~alang/onsc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res*, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, *Crystal Structure Comm.*, Intn'l Union of Crystallography, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.



## US 9,301,920 B2

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(56)

## References Cited

## OTHER PUBLICATIONS

- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gisia L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Prodynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Prodynova%20TS%20100%2012%20Patches\_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Salole, Eugene G., Estradiol, *Analytical Profiles of Drug Substances*, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Base . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, SciFinder, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A. E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- SciFinder Scholar Prednisone Chemical Properties, SciFinder, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, SciFinder, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, SciFinder, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), *Crystal Structure Comm.*, vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Saffey Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of Thevetia peruviana and Hura crepitans Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopocia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, [http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index\[2/3/20141:37:50 PM\]](http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index[2/3/20141:37:50 PM]).
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.
- Corn Refiners Assoc, Corn Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Egbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.
- Ferrari, Roseli AP, et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, Piracicaba, Braz.
- Gunstone, Frank D, et al., Vegetable Oils in Food Technology: Composition, Properties and Uses, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, *Springerlink.com*, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science*, vol. 47, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Lauroyl Polyoxylglycerides, Saffey Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate-Corn Oil, Lot G0L404, Jul. 2013.
- Weber, E.J., Corn Lipids, *Cereal Chem.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- Abbas et al., Regression of endometrial implants treated with vitamin D3 in a rat model of endometriosis, *European J of Pharma*, 715 (2013) 72-75, Elsevier.
- Abitec, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.
- Alvarez et al., Ectopic uterine tissue as a chronic pain generator, *Neuroscience*, Dec. 6, 2012, 225: 269-272.
- Application Note FT-IR: JI-Ap-FT0508-008, CD spectra of pharmaceuticals substances—Steroids (2), JASCO International Co., Ltd., 2 pages.
- Archer et al., Effects of ospemifene on the female reproductive and urinary tracts: translation from preclinical models into clinical evidence, *Menopause: The Journal of the North American Menopause Society*, vol. 22, No. 77, pp. 1-11 (2015).
- Archer et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study, *Advances in Therapy®*, vol. 9 No. 1, Jan./Feb. 1992.
- Ashburn et al., Cardiovascular, Hepatic and Renal Lesions in Mice Receiving Cortisone, Estrone and Progesterone, *Yale J Biology and Medicine*, vol. 35, Feb. 1963, pp. 329-340.
- Bartosova, Transdermal Drug Delivery In Vitro Using Diffusion Cells, *Current Medicinal Chemistry*, 2012, 19, 4671-4677, Bentham Science Publishers.
- Benbow et al., Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus during Rat Pregnancy, *Biology of Reproduction* 52, 1327-1333 (1995).

## US 9,301,920 B2

Page 14

(56)

## References Cited

## OTHER PUBLICATIONS

- Blake et al., Single and multidose pharmacokinetic study of a vaginal micronized progesterone insert (Endometrin) compared with vaginal gel in healthy reproductive aged female subjects, *Fertility and Sterility* vol. 94, No. 4, Sep. 2010, Elsevier.
- Christen et al., Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin, *J Clin Oncol* 11:2417-2426, 1993.
- Christensson et al., Limonene hydroperoxide analogues differ in allergenic activity, *Contact Dermatitis* 2008; 59: 344-352.
- Christensson et al., Limonene hydroperoxide analogues show specific patch test reactions, *Contact Dermatitis*, 70, 291-299, 2014.
- Christensson et al., Positive patch test reactions to oxidized limonene: exposure and relevance, *Contact Dermatitis*, 71, 264-272, 2014.
- Cicinelli et al., Direct Transport of Progesterone From Vagina to Uterus, *Obstetrics & Gynecology*, vol. 95, No. 3, Mar. 2000, pp. 403-406.
- Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," *Southern Medical Journal*, vol. 107, No. 7, Jul. 2014, pp. 433-436.
- Critchley et al., Estrogen Receptor  $\beta$ , But Not Estrogen Receptor  $\alpha$ , Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium, *The Journal of Clinical Endocrinology & Metabolism*, 2001, vol. 86, No. 3, pp. 1370-1378.
- Du et al., Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood, *Menopause: The Journal of the North American Menopause Society*, 2013, vol. 20, No. 11, pp. 1-7.
- Engelhardt et al., Conceptus Influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy, *Biology of Reproduction* 66, 1875-1880 (2002).
- Ettinger et al., Comparison of endometrial growth produced by unopposed conjugated estrogens or by micronized estradiol in postmenopausal women, *Am J Obstet Gynecol* 1997; 176:112-117.
- Excipients for Pharmaceuticals, Sasol Olefins & Surfactants GmbH, 2010, 28 pages.
- Filipsson et al., Concise International Chemical Assessment Document 5: Limonene, first draft, World Health Organization, Geneva, 1998, 36 pages.
- Final Report on the Safety Assessment of BHT, *International Journal of Toxicology*, 21(Suppl. 2):19-94, 2002/.
- Flyvholm, Sensitizing risk of butylated hydroxytoluene based on exposure and effect data, *Contact Dermatitis* 1990; 23: 341-345.
- Franklin et al., Characterization of immunoglobulins and cytokines in human cervical mucus: influence of exogenous and endogenous hormones, *Journal of Reproductive Immunology* 42 (1999) 93-106, Elsevier.
- Franz et al., Use of Excised Human Skin to Assess the Bioequivalence of Topical Products, *Skin Pharmacol Physiol* 2009;22:276-286.
- Furness et al., Hormone therapy in postmenopausal women and risk of endometrial hyperplasia (Review), 2012, pp. 1-204, *The Cochrane Collaboration*. Published by John Wiley & Sons, Ltd.
- Gäfvert et al., Free radicals in antigen formation: reduction of contact allergic response to hydroperoxides by epidermal treatment with antioxidants, *British Journal of Dermatology* 2002; 146: 649-656.
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Gattefossé, "Excipients for Safe and Effective Topical Delivery, Drug Development and Delivery" Jul./Aug. 2012, <http://drug-dev.com/Main/Back-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#>.
- Geelen, Math J.H. et al., "Dietary medium-chain fatty acids raise and (n-3) polyunsaturated fatty acids lower hepatic triacylglycerol synthesis in rats," *The Journal of Nutrition*, 1995, 125(10):2449-2456.
- Gillet et al., Induction of amenorrhea during hormone replacement therapy: optimal micronized progesterone dose. A multicenter study, *Maturitas* 19 (1994) 103-115.
- Glaser et al, Pilot Study: Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina, *Gynecol Obstet Invest* 2008;66:111-118.
- Golatowski et al., Comparative evaluation of saliva collection methods for proteome analysis, *Clinica Chimica Acta* 419 (2013) 42-46.
- Graham et al, Physiological Action of Progesterone in Target Tissues, *Endocrine Reviews*, 1997, vol. 18, No. 4, pp. 502-519.
- Groothuis et al., Estrogen and the endometrium: lessons learned from gene expression profiling in rodents and human, *Human Reproduction Update*, vol. 13, No. 4 pp. 405-417, 2007.
- Hamid et al., The effects of common solubilizing agents on the intestinal membrane barrier functions and membrane toxicity in rats, *International Journal of Pharmaceutics* 379 (2009) 100-108, Elsevier.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," *Clinical Pharmacy*, 1990, vol. 9, No. 5, pp. 366-371.
- He et al., Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia Induced by Ovariectomy Combined with Estrogen, *Gynecol Obstet Invest* 2013;76:51-56.
- Helmy et al., Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats, *Clinic Pharmacol Biopharmaceut*, 2014, S2, 7 pages.
- Herman, Anna et al., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," 2014 Royal Pharmaceutical Society, *Journal of Pharmacy and Pharmacology*, pp. 1-13.
- Hostynek, JJ, Predicting absorption of fragrance chemicals through human skin, *J. Soc. CosmeT. hem.*, 4 6, 221-229 (Jul./Aug. 1995).
- Hurn et al., Estrogen as a Neuroprotectant in Stroke, *Journal of Cerebral Blood Flow and Metabolism* 20:631-652, 2000, Lippincott Williams & Wilkins, Inc., Philadelphia.
- Hyder et al., Synthetic Estrogen 17 $\alpha$ -Ethinyl Estradiol Induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17 $\beta$ -Estradiol, *JPET* 290(2):740-747, 1999.
- Joshi et al., Detection and synthesis of a progestagen-dependent protein in human endometrium, *J Reprod Fert* (1980) 59,273-285.
- Kanno et al., The OECD Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses: Phase 1, *Environmental Health Perspectives* • vol. 109 | No. 8 | Aug. 2001, pp. 785-794.
- Karlberg et al., Air oxidation of d-limonene (the citrus solvent) creates potent allergens, *Contact Dermatitis*, 1992; 26: 332-340.
- Karlberg et al., Influence of an anti-oxidant on the formation of allergenic compounds during auto-oxidation of d-limonene, *Ann. Occup. Hyg.*, vol. 38, No. 2, pp. 199-207, 1994.
- Kaunitz, Andrew M., Extended duration use of menopausal hormone therapy, *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 6, pp. 1-3.
- Kharode et al., The Pairing of a Selective Estrogen Receptor Modulator, Bazedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention, *Endocrinology* 149(12):6084-6091, 2008.
- Kim et al., Safety Evaluation and Risk Assessment of d-Limonene, *Journal of Toxicology and Environmental Health, Part B: Critical Reviews*, 2013, 16:1, 17-38 <http://dx.doi.org/10.1080/10937404.2013.769418>.
- Koga et al., Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate, *European Journal of Pharmaceutics and Biopharmaceutics* 64 (2006) 82-91.
- Komm et al., Bazedoxifene Acetate: A Selective Estrogen Receptor Modulator with Improved Selectivity, *Endocrinology* 146(9):3999-4008, 2005.
- Kumasaka et al., Effects of Various Forms of Progestin on the Estrogen-Primed, Ovariectomized Rat, *Endocrine Journal* 1994, 41(2), 161-169.

## US 9,301,920 B2

Page 15

(56)

## References Cited

## OTHER PUBLICATIONS

- Kuon et al., A Novel Optical Method to Assess Cervical Changes during Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor, *Am J Obstet Gynecol.* Jul. 2011; 205(1): 82.e15-82.e20.
- Kuon et al., Actions of progestins for the inhibition of cervical ripening and uterine contractions to prevent preterm birth, *FVV in OBGYN*, 2012, 4 (2): 110-119.
- Kuon et al., Pharmacological actions of progestins to inhibit cervical ripening and prevent delivery depend upon their properties, the route of administration and the vehicle, *Am J Obstet Gynecol.* May 2010; 202(5): 455.e1-455.e9.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," *Journal of Pharmaceutical Sciences*, vol. 86, No. 1, Jan. 1997, pp. 13-18.
- Leonetti et al., Transdermal progesterone cream as an alternative progestin in hormone therapy, *Alternative Therapies*, Nov./Dec. 2005, vol. 11, No. 6, pp. 36-38.
- López-Belmonte, Corrigendum to "Comparative uterine effects on ovariectomized rats after repeated treatment with different vaginal estrogen formulations" [*Maturitas* 72 (2012) 353-358], *Maturitas* 74 (2013) 393, Elsevier.
- Madishetti et al., Development of domperidone bilayered matrix type transdermal patches: physicochemical, in vitro and ex vivo characterization, *DARU* vol. 18, No. 3, 2010, pp. 221-229.
- Manson, JoAnn E. et al., "Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials," *JAMA*, Oct. 2, 2013, vol. 310, No. 13, pp. 1353-1368.
- Miles et al., Pharmacokinetics and endometrial tissue levels of progesterone after administration by Intramuscular and vaginal routes: a comparative study, *Fertility and Sterility*, vol. 62, No. 3, Sep. 1994, pp. 485-490.
- Miller et al., Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast, *Journal of Cancer Therapy*, 2012, 3, 749-754.
- Nilsson et al., Analysis of Contact Allergenic Compounds in Oxidized d-Limonene, *Chromatographia* vol. 42, No. 3/4, Feb. 1996, pp. 199-205.
- Opinion on the Diethylene Glycol Monoethyl Ether (DEGEE), Scientific Committee on Consumer Products, Dec. 19, 2006, 27 pages.
- Outterson, K., The Drug Quality and Security Act—Mind the Gaps, *n engl j med* 370;2 *nejm.org* Jan. 9, 2014, pp. 97-99.
- Palamakula et al., Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components, *Pharmaceutical Technology* Oct. 2004, pp. 74-88.
- Parasuraman et al., Blood sample collection in small laboratory animals, *Journal of Pharmacology & Pharmacotherapeutics* | Jul.-Dec. 2010 | vol. 1 | Issue 2, pp. 87-93.
- Pfaus et al., Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist, *PNAS*, Jul. 6, 2004, vol. 101, No. 27, pp. 10201-10204.
- Pickles, VR, Cutaneous reactions to injection of progesterone solutions into the skin, *Br Med Journal*, Aug. 16, 1952, pp. 373-374.
- Pinkerton et al., What are the concerns about custom-compounded "bioidentical" hormone therapy? *Menopause: The Journal of the North American Menopause Society*, vol. 21, No. 12, 2014, pp. 1-3.
- Portman, David et al., One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy, *Menopause*, vol. 22, No. 11, 2015, pp. 000/000 (8 pages).
- Prausnitz et al., Transdermal drug delivery, *Nat Biotechnol.* Nov. 2008; 26(11): 1261-1268.
- Product Safety Assessment: Diethylene Glycol Monoethyl Ether, Created: Sep. 24, 2007 The Dow Chemical Company Page, 5 pages.
- Provider Data Sheet, About Dried Blood Spot Testing, ZRT Laboratory, 2014, 3 pages.
- Rahn et al., Vaginal Estrogen for Genitourinary Syndrome of Menopause a Systematic Review, *Obstet Gynecol* 2014;124(6):1147-56.
- Rao, Rajeswara et al., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *J Bioequiv Availab.* 2014;6: 139-143.
- Reisman et al., Topical Application of the Synthetic Triterpenoid RTA 408 Protects Mice from Radiation-Induced Dermatitis, *Radiation Research* 181,512-520 (2014).
- Ross et al., Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women, *AnnJ Obstet Gynecol*, Oct. 1997, vol. 177, No. 4, pp. 937-941.
- Ruan et al., Systemic progesterone therapy—Oral, vaginal, injections and even transdermal? *Maturitas* 79 (2014) 248-255, Elsevier.
- Salem, HF, Sustained-release progesterone nanosuspension following intramuscular injection in ovariectomized rats, *International Journal of Nanomedicine* 2010;5 943-954, Dove Press.
- Santen, RJ, Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels, *Climacteric* 2014;17:1-14.
- Schindler, Aldof E. et al., Classification and pharmacology of progestins, *Maturitas* 46S1 (2003) S7-S16.
- Schutte et al., A tissue engineered human endometrial stroma that responds to cues for secretory differentiation, decidualization and menstruation, *Fertil Steril.* Apr. 2012; 97(4): 997-1003, Elsevier.
- Schweikart et al., Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats, *Toxicologic Pathology*, 42: 1188-1196, 2014.
- Shao et al., Review Open Access Direct effects of metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma, *Journal of Experimental & Clinical Cancer Research* 2014, 33(1):41, 11 pages.
- Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," *Journal of Adolescent Health*, 2003; 32:183-186.
- Siew, Adeline, moderator, Bioavailability Enhancement with Lipid-Based Drug-Delivery Systems, *Pharmaceutical Technology*, Aug. 2014, pp. 28, 30-31.
- Simon, James A., What if the Women's Health Initiative had used transdermal estradiol and oral progesterone instead? *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 7, pp. 1-15.
- Sitruk-Ware, Regine, "Pharmacological profile of progestins," *Maturitas* 47 (2004) 277-283.
- Smyth et al., Summary of Toxicological Data, A 2-Yr Study of Diethylene Glycol Monoethyl Ether in Rats, *Fd Cosmet. Toxicol.* vol. 2, pp. 641-642, 1964.
- Stanczyk et al., Therapeutically equivalent pharmacokinetic profile across three application sites for AG200-15, a novel low-estrogen dose contraceptive patch, *Contraception*, 87 (2013) pp. 744-749.
- Stanczyk, F.Z. et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," *Menopause: The Journal of the North American Menopause Society*, 2005, vol. 12, No. 2, pp. 232-237.
- Stanczyk, F.Z., "All progestins are not created equal," *Steroids* 68 (2003) 879-880.
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective?" *Climacteric* 2014; 17(Suppl 2):8-11.
- Stephenson et al., "Transdermal progesterone: Effects on Menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women," *Int J Pharmaceutical Compounding*, vol. 12, No. 4, Jul./Aug. 2008, pp. 295-304.
- Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," *Food and Chemical Toxicology*, 72 (2014) pp. 40-50.
- Sun, Jidong, D-Limonene: Safety and Clinical Applications, *Alternative Medicine Review* vol. 12, No. 3, 2007, pp. 259-264.
- Tang et al., Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat, *Biology of Reproduction* 31, 399-413 (1984).



## US 9,301,920 B2

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(56)

## References Cited

## OTHER PUBLICATIONS

- Tas et al., Comparison of antiproliferative effects of metformine and progesterone on estrogen-induced endometrial hyperplasia in rats, *Gynecol Endocrinol*, Early Online: 1-4, 2013. <http://informahealthcare.com/gye>.
- Thomas, Peter, Characteristics of membrane progesterin receptor alpha (mPR $\alpha$ ) and progesterone membrane receptor component 1 (PGRMC1) and their roles in mediating rapid progesterin actions, *Frontiers in Neuroendocrinology* 29 (2008) 292-312.
- Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," *Journal of Pharmaceutical Sciences*, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.
- Ueda et al., Topical and Transdermal Drug Products, *Pharmacoepial Forum*, vol. 35(3) [May-Jun. 2009], 750-754.
- U.S. Appl. No. 12/561,515 Jan. 29, 2013 Advisory Action (Opera 1.1)
- USPTO Final Office Action dated Oct. 26, 2012 in U.S. Appl. No. 12/561,515 (Opera 1.1).
- USPTO Notice of Allowance dated Sep. 11, 2013 in U.S. Appl. No. 12/561,515 (Opera 1.1).
- USPTO Office Action dated Dec. 12, 2011 in U.S. Appl. No. 12/561,515 (Opera 1.1).
- U.S. Appl. No. 13/843,362 Mar. 16, 2015 Restriction Requirement.
- U.S. Appl. No. 14/099,545 Jul. 14, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,562 Mar. 27, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/099,562 Jul. 2, 2014 Final Office Action.
- U.S. Appl. No. 14/099,562 Dec. 10, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,571 Mar. 28, 2014 Restriction Requirement.
- U.S. Appl. No. 14/099,571 Jul. 15, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,582 Apr. 29, 2014 Restriction Requirement.
- U.S. Appl. No. 14/099,582 Jun. 17, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/099,582 Nov. 7, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,582 Jan. 22, 2015 Notice of Allowance.
- U.S. Appl. No. 14/099,598 May 13, 2014 Restriction Requirement.
- U.S. Appl. No. 14/099,598 Jul. 3, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/099,598 Dec. 10, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,612 Mar. 20, 2014 Restriction Requirement.
- U.S. Appl. No. 14/099,612 Oct. 30, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/099,612 Nov. 26, 2014 Notice of Allowance.
- U.S. Appl. No. 14/099,623 Jul. 18, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/099,623 Dec. 15, 2014 Notice of Allowance.
- U.S. Appl. No. 14/103,355 Dec. 8, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/106,655 Jul. 3, 2014 Restriction Requirement.
- U.S. Appl. No. 14/125,554 Dec. 5, 2014 Restriction Requirement.
- U.S. Appl. No. 14/125,554 Apr. 14, 2015 Non-Final Office Action.
- U.S. Appl. No. 14/136,048 Nov. 4, 2014 Restriction Requirement.
- U.S. Appl. No. 14/136,048 Mar. 12, 2015 Non-Final Office Action.
- U.S. Appl. No. 14/475,814 Oct. 1, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/475,814 Feb. 13, 2015 Notice of Allowance.
- U.S. Appl. No. 14/475,864 Feb. 11, 2014 Notice of Allowance.
- U.S. Appl. No. 14/475,864 Oct. 2, 2014 Non-Final Office Action.
- U.S. Appl. No. 14/476,040 Mar. 26, 2014 Restriction Requirement.
- U.S. Appl. No. 14/521,230 Dec. 5, 2014 Restriction Requirement.
- U.S. Appl. No. 14/521,230 Feb. 18, 2015 Non-Final Office Action.
- U.S. Appl. No. 14/624,051 Apr. 7, 2015 Non-Final Office Action.
- Voegtline et al., Dispatches from the interface of salivary bioscience and neonatal research, *Frontiers in Endocrinology*, Mar. 2014, vol. 5, article 25, 8 pages.
- Waddell et al., Distribution and metabolism of topically applied progesterone in a rat model, *Journal of Steroid Biochemistry & Molecular Biology* 80 (2002) 449-455.
- Waddell et al., The Metabolic Clearance of Progesterone in the Pregnant Rat: Absence of a Physiological Role for the Lung, *Biology of Reproduction* 40, 1188-1193 (1989).
- Walter et al., The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice, *Reproduction* (2005) 129 765-777.
- Weintraub, Arlene, "Women fooled by untested hormones from compounding pharmacies," *Forbes*, Feb. 20, 2015; retrieved online at <http://onforbes.com/1LIUm1V> on Feb. 23, 2015, 3 pages.
- Wren et al., Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women, *Climacteric*, 2000, 3(3), pp. 155-160. <http://dx.doi.org/10.1080/13697130008500109>.
- Wu et al., Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus, *Biology of Reproduction* 69, 1308-1317 (2003).
- Zava, David T. et al., Percutaneous absorption of progesterone, *Maturitas* 77 (2014) 91-92, Elsevier.
- Zava, David T., Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues, Script, ZRT Laboratory, pp. 4-5. [http://www.zrtlab.com/component/docman/cat\\_view/10-publications?Itemid](http://www.zrtlab.com/component/docman/cat_view/10-publications?Itemid).
- Fusun Acarturk, "Mucoadhesive Vaginal Drug Delivery System," Recent Patents on Drug Delivery & Formulation, 3(3):193-205, 2009.
- Katie O. Fuchs et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," *Aesthetic Dermatology*, 8(1):14-19, 2006.
- Nick Panay et al., "The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy," DOI: 0.1177/1754045313489645, [min.sagepub.com](http://min.sagepub.com).
- Menopause International: The Integrated Journal of Postreproductive Health 0(0):1-10, 2013.
- Bhavnani et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," *J Clin Endocrinol Metab.* doi:10.1210/jc.2011-2492, 97(3):0000-0000, 2011, 4 pages.
- Du et al., "Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood," *Menopause: The Journal of the North American Menopause Society*, doi: 10.1097/gme.0b013e31828d39a2, 20(11):0000-0000, 2013, 7 pages.
- Patel et al., "Transdermal Drug Delivery System: A Review," *The Pharma Innovation*, 1(4):78-87, 2012.
- Sarrel et al., "The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years," *American Journal of Public Health, Research and Practice*, e1-e6. doi:10.2105/AJPH.2013.301295, 2013.
- Sitruk-Ware, "Progestogens in hormonal replacement therapy: new molecules, risks, and benefits," *Menopause: The Journal of the North American Menopause Society*, 9(1):6-15, 2002.
- Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002, 13 pages.
- Bhavnani et al., "Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ER $\alpha$  and ER $\beta$ ," *Endocrinology* 2008;149(10):4857-4870.
- Hargrove et al., "Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronize Estradiol and Progesterone," *Obstetrics & Gynecology: Estrogen Replacement Therapy* 1989;73(4):606-612.
- Stanczyk et al., "Ethinyl estradiol and 17 $\beta$ -estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment," *Elsevier* 2013;87:706-727.
- Wood et al., "Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys," *Breast Cancer Res Treat* 2007;101:125-134.
- Fotherby, "Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy," *Elsevier* 1996;54:59-69.
- Kincl et al., "Increasing Oral Bioavailability of Progesterone by Formulation," *Journal of Steroid Biochemistry* 1978;9:83-84.
- Nams "Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society," *Menopause: The Journal of the North American Menopause Society* 2013;20(9):888-902.

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---

(56)

**References Cited**

OTHER PUBLICATIONS

Shufelt et al., "Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study," *Menopause: The Journal of the North American Menopause Society* 2013;DOI: 10.1097/GME.0b013e31829a64f9:1-7.

Sitruk-Ware et al., "Oral Micronized Progesterone—Bioavailability pharmacokinetics, pharmacological and therapeutic implications—A review," *Contraception* 1987;36(4):373-402.

Smith et al., "Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens," *JAMA Internal Medicine* 2013;doi:10.1001/jamainternmed.2013.11074:E1-E7.

Whitehead et al., "Absorption and metabolism of oral progesterone," *British Medical Journal* 1980:825-827.

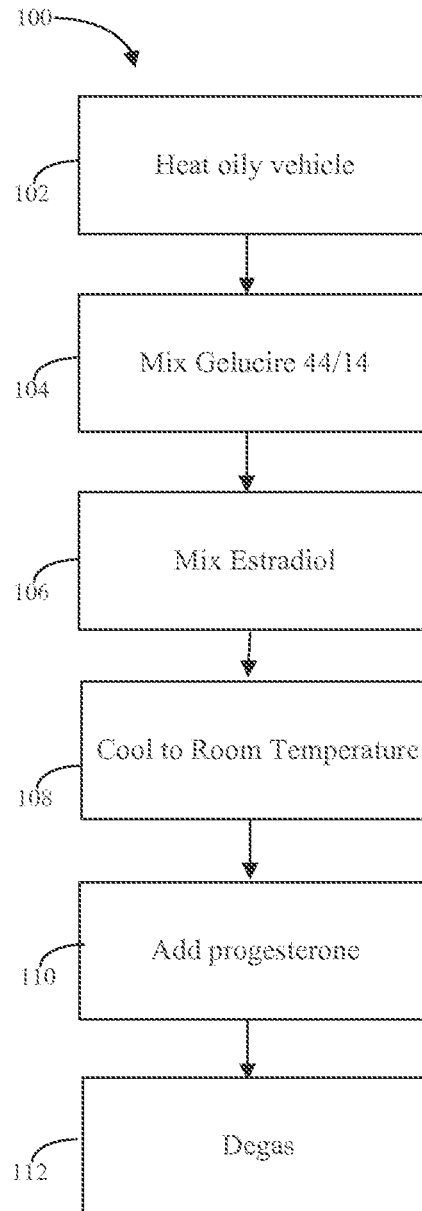
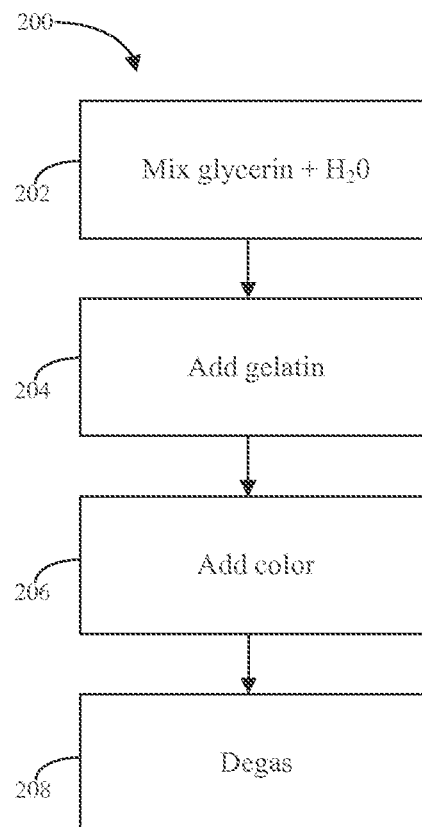
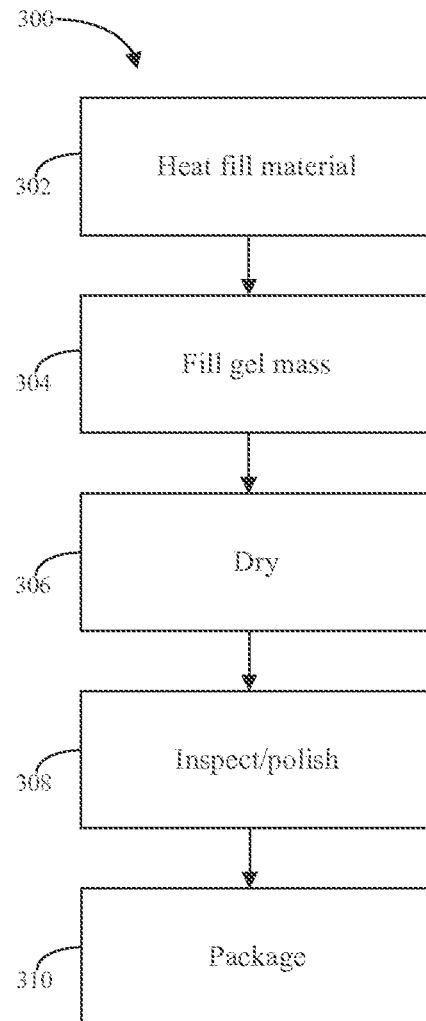


Fig. 1





**Fig. 2**



**Fig. 3**

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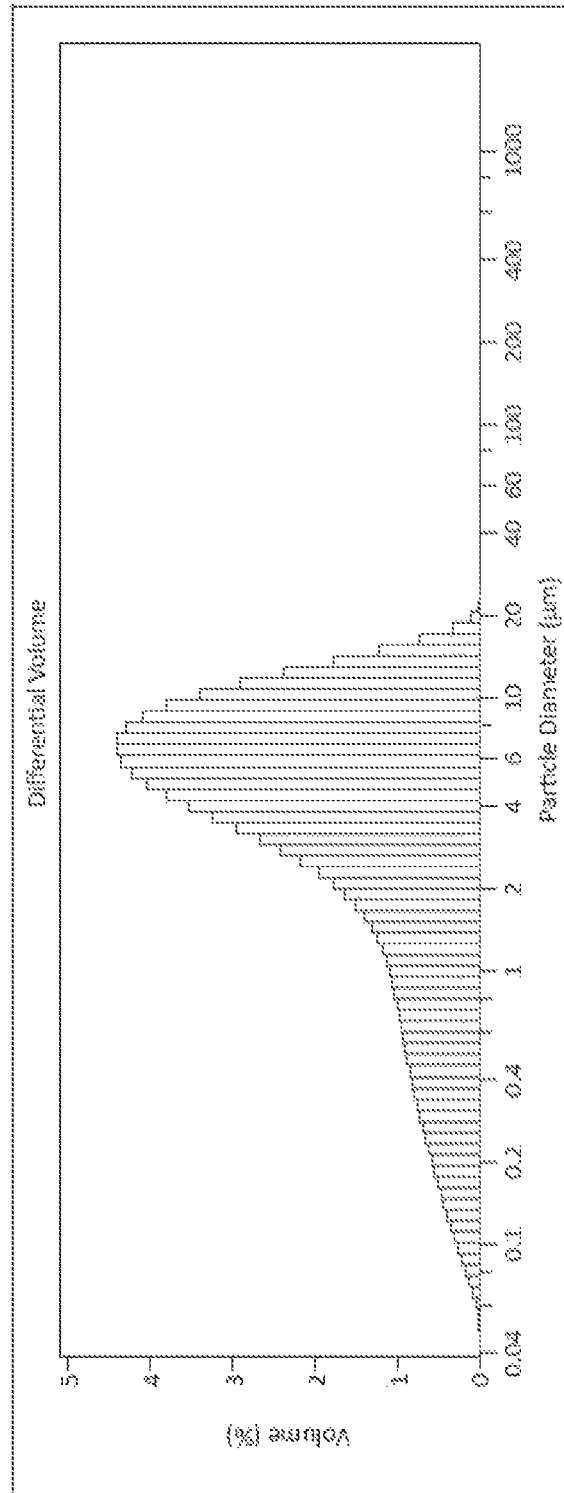


FIG. 4

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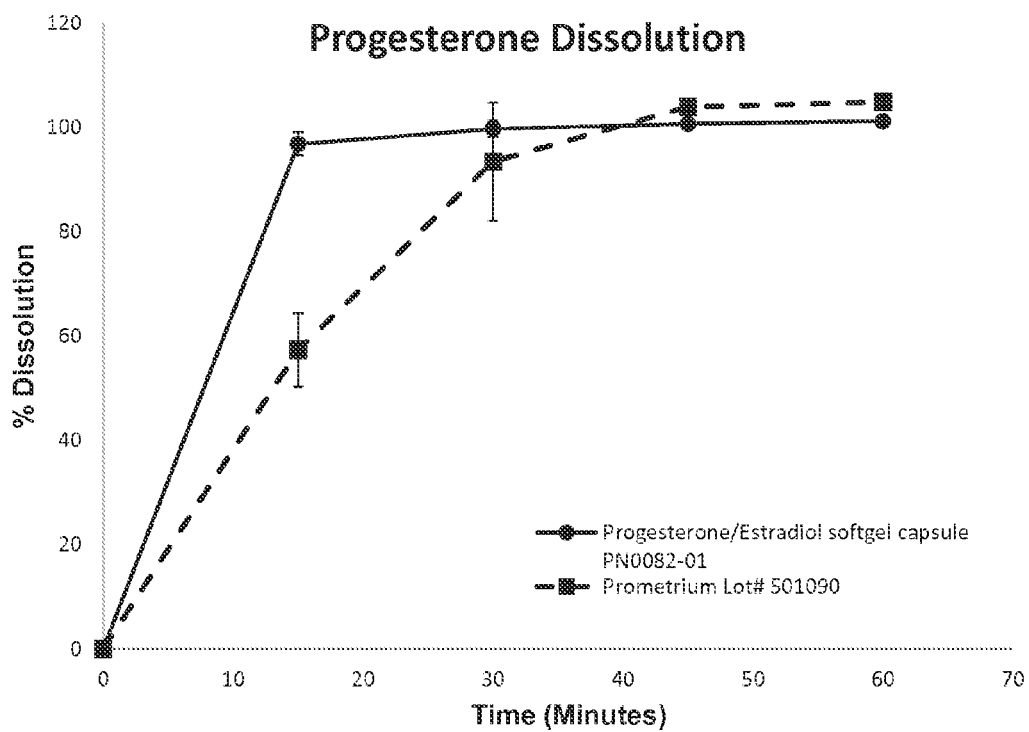
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FIG. 5

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# **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

## **CROSS REFERENCE TO RELATED APPLICATIONS**

This application claims priority to the following U.S. patent applications: U.S. application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT THERAPIES," which was filed on Nov. 21, 2012; U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; and U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULA- TIONS," which was filed on Jun. 20, 2012. All aforementioned applications are hereby incorporated by reference herein in their entirety.

## **BACKGROUND**

### **1. Field**

This disclosure relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient States, each as herein below defined.

### **2. Discussion of the Related Art**

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific disease states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening), reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "continuous-combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

"Bio-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bod-

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ies can be used and are often referred to as natural hormone replacement therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occur naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as Prometrium® (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc (New York). Prometrium was approved for sale in the United States on May 14, 1998 under NDA # NO19781. According to the prescribing information approved for this product (Rev June 2009) ("Prometrium prescribing information"), Prometrium comprises synthetic progesterone that is chemically identical to progesterone of human ovarian origin. Capsules comprise 100 mg or 200 mg of micronized progesterone. The inactive ingredients include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, and yellow and red dyes.

Other products such as Prempro® and Premphase® (Wyeth Laboratories, a division Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing Premarin (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

## **SUMMARY**

According to various embodiments of the disclosure, natural hormone replacement therapies are provided comprising cyclic/sequential and continuous-combined delivery via pharmaceutical formulations of solubilized estradiol and micronized and/or partially or completely solubilized progesterone. Estradiol and micronized and/or partially or completely solubilized progesterone delivered together daily can be combined in either a single unit dose or in separate unit doses, typically in a soft capsule. A 28-day or monthly regimen of tablets or capsules can be packaged in a single blister pack having delivery days identified to improve compliance. Various examples formulations of natural hormones, and the use of these formulations for hormone replacement therapies, each in accordance with the invention are set forth below.

## **BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES**

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. 1 illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments;

FIG. 2 illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments;

FIG. 3 illustrates an exemplary manufacturing process in accordance with various embodiments; and

FIG. 4 illustrates a graph of the particle distribution obtained in Example 10.

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FIG. 5 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

#### DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone, or dosage forms that provide greater consistency of absorption of progesterone among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

#### Definitions

The term “micronized progesterone,” as used herein, includes micronized progesterone having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns.

The term “X50,” as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in a dissolution test compared to Prometrium at a similar dosage strength and the same USP dissolution apparatus.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone or estradiol or estrone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (pK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC, Cmax, and optionally, Tmax.

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone, estradiol or estrone over time.

The term, “Cmax” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone, estradiol or estrone over time.

The term, “Tmax” as used herein, refers to the time that it takes for progesterone, estradiol or estrone blood concentration to reach the maximum value.

Collectively AUC, Cmax and, optionally, Tmax are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal especially a mammal, including human, subject.

The term “solubilizer,” as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without

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limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term “excipients,” as used herein, refer to non-active pharmaceutical ingredients (“API”) substances such as carriers, solvents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “oil” as used herein may be any pharmaceutically acceptable substance, such as an organic oil other than peanut oil, that would suspend and/or solubilize any suitable progesterone, starting material, or precursor, including micronized progesterone as described herein. More specifically, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, and triglyceride, or derivatives thereof, or combinations thereof.

“Fully solubilized progesterone” as used herein means progesterone which is about 100% in solution, i.e., at least 98% in solution.

“Partially solubilized progesterone” as used herein means progesterone which is in any state of solubilization up to but not including about 100%, i.e., up to but not including 98% in solution.

As used herein, unless specified, estradiol includes estradiol in anhydrous and hemihydrate forms.

#### Description

Provided herein are the following formulations: solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; and solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be



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desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution is from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %; estradiol is 0.1 to 0.8 wt %, e.g., 0.15 to 0.35 wt %.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of Prometrium. Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

According to the Prometrium prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered Prometrium once a day for five days resulted in the mean PK parameters listed in the following table:

Parameter	Prometrium Capsules Daily Dose		
	100 mg	200 mg	300 mg
$C_{max}$ (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
$T_{max}$ (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
$AUC_{0-10}$ (ng x hr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

In a particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of Prometrium at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to Prometrium can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure includes the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, "Progesterone-deficient States"); and the use of formulations

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as described herein wherein estradiol is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans, having menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental estrogen. (collectively, "Estrogen-deficient States"), each in a subject in need of treatment, and each with a non-toxic effective amount of said formulations. As used herein, the term "treatment", or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as  $17\beta$ -estradiol and E2) and a natural progestin is progesterone. An exemplary cyclic/sequential regimen comprises delivery of from about 0.125 mg to about 2.0 mg of estradiol daily for 14-18 days, followed by delivery of from about 0.125 mg to about 2 mg of estradiol and about 25 mg to about 200 mg of progesterone daily for 10-14 days. Cyclic/sequential regimens may be especially useful for menopausal females. Other exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Other exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017  $\mu$ m to 2000  $\mu$ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery

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and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4  $\mu$ m to 2000  $\mu$ m. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

Each of estradiol and progesterone as described herein can be formulated alone pursuant to the teachings below. These formulations can be prepared for oral administration or can be combined, based on compatibility, for co-administration of estradiol and progesterone in a single oral unit dosage form.

Progesterone formulations of the present disclosure are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, anti-oxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of caproic fatty acid; caprylic fatty acid; capric fatty acid; tauric acid; myristic acid; linoleic acid; succinic acid; glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (Miglyol®; SASOL Germany GMBH, Hamburg; Miglyol includes Miglyol 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the Capmul brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (Capmul MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: Transcutol); diethylene glycol monoethyl ether; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

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In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: Transcutol and Miglyol; Transcutol, Miglyol and Capmul PG 8 and/or PG 10; Capmul MCM; Capmul MCM and a non-ionic surfactant; and Capmul MCM and Gelucire.

Various ratios of these oils can be used for full solubilization of progesterone. Capmul MCM and a non-ionic surfactant, e.g., Gelucire 44/14, can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, Capmul MCM and Gelucire were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. See, e.g., Tables 13-17, below. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1. Among other combinations, these oils and/or solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose is generally limited only by the practical size of the final dosage form.

In illustrative embodiments of the invention, oils used to solubilize estradiol and to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, estradiol or progesterone (or both) is soluble in the oils at room temperature, although it may be desirable to warm the oils up until they are in a liquid state. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50 C., e.g., at or below 50 C., at or below 40 C., or at or below 50 C. In illustrative embodiments, Gelucire 44/14 is heated to about 65 C. and Capmul MCM is heated to about 40 C. to facilitate mixing of the oil and non-surfactant, although such heating is not necessary to dissolve the estradiol or progesterone. In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8 wt % or higher, or 1.0 wt % or higher.

Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, Capmul MCM, Capmul MCM C10, Capmul MCM C8, and Capmul MCM C8 EP. These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, Miglyol 810 and Miglyol 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, Capmul PG-8, Capmul PG-2L EP/NF, Capmul PG-8 NF, Capmul PG-12 EP/NF and Capryol. Other illustrative examples include Miglyol 840.

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others, Gelucire 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

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Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of Gelucire, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids. Specifically, a product information sheet for Myglyol by SASOL provides as the composition of fatty acids as follows:

	Tests				
	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic acid (C14:0)	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

It will be understood that oils are often mixtures. So, for example, when an oil is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for Capmul MCM C8 describes Capmul MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher,

Mixtures of medium chain fatty acid glycerides, e.g., C6-C12, C8-C12, or C8-C10 fatty acid mono- and diglycerides or mono-, di-, and triglycerides are very well suited for dissolving estradiol; good results have been obtained with an oil that is predominantly a mixture of C8-C10 saturated fatty acid mono- and diglycerides. Longer chain glycerides appear to be not as well suited for dissolution of estradiol. On the other hand, high solubility of progesterone has been obtained in mixtures that are predominantly medium chain fatty acid triglycerides.

High solubility of estradiol has been obtained in 2-(2-Ethoxyethoxy)ethanol, e.g., Transcutol and in Propylene glycol monocaprylate, e.g., Capryol™ 90 (Gattefosse).

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone or estradiol. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., Capmul MCM) and polyethylene glycol glycerides (e.g., Gelucire) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65 C. in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature or at lower temperatures as the mixture cools or even after it has cooled as temperatures above room temperature, e.g., about 20 C., are not required to solubilize the estradiol in preferred oils. The progesterone can also be added as the mixture cools, e.g., to below about 40 C. or to below about 30 C., even down to room temperature.

In various embodiments, estradiol is solubilized. Solubilized estradiol may include estradiol that is approximately: 90% soluble in a solvent; 93% soluble in a solvent; 95% soluble in a solvent; 97% soluble in a solvent; 99% soluble in a solvent; and 100% soluble in a solvent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %).

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In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In addition to the oils referenced above for progesterone, which can also be used as solubilizers for estradiol, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid esters or alcohols. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as Gelucire, including, for example, Gelucire 44/11 and Gelucire 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, Gelucire 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, e.g., Tables 13-17, below. Other non-ionic surfactants include, e.g., Labrasol® PEG-8 Caprylic/Capric Glycerides (Gattefosse) and Labarafil® corn/apricot oil PEG-6 esters (Gattefosse).

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable anti-oxidant may be used such as, for example and without limitation butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formula-

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tions of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises solubilized estradiol, progesterone at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of glycerol, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with Gelucire as surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following four formulations:

Formulation A - P:50/EE:0.25:

Ingredient(s)	Amount (%) w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.17	0.26
Capmul MCM, NF	65.49	98.24
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00

Formulation B - P:50/EE:0.5:

Ingredient(s)	Amount (%) w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.35	0.52
Capmul MCM, NF	65.32	97.98
Gelucire 44/14, NF	1.00	1.50
Total	100.00	150.00

Formulation C - P:100/EE:0.5:

Ingredient(s)	Amount (%) w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.17	0.52
Capmul MCM, NF	65.49	196.48
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00

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Formulation D - P:100/EE:1:

Ingredient(s)	Amount (%) w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.34	1.03
Capmul MCM, NF	65.32	195.97
Gelucire 44/14, NF	1.00	3.00
Total	100.00	300.00

Formulation E - P:200/EE:2:

Ingredient(s)	Amount (%) w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate	0.34	2.06
Capmul MCM, NF	65.32	391.94
Gelucire 44/14, NF	1.00	6.00
Total	100.00	600.00

\*Note:

1.00 mg Estradiol equivalent to 1.03 mg Estradiol Hemihydrate.

In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono- and diglycerides, such as Capmul MCM, and 0.5 to 10 wt % non-ionic surfactant, such as Gelucire 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opatint red and white, and, optionally, Miglyol 812.

Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g., 75%, 80%, 85%, 90%, or >95%, is solubilized appear to provide improved PK-related properties.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.



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Orally administered formulations of the present disclosure containing micronized and/or partially solubilized, or fully solubilized, progesterone are also used for the treatment of endometrial hyperplasia, secondary amenorrhea and other disease states treated with supplemental progesterone. Generally, progesterone-containing formulations described herein are used to treat the effects of the administration of supplemental estrogen whether administered alone or in combination with solubilized estradiol of the present disclosure or other estrogen-containing formulations. In various other embodiments, a capsule containing formulations of the present disclosure, for example a softgel capsule, may be applied in or around the vagina.

Formulations of the present disclosure containing solubilized estradiol are used to treat Estrogen-deficient States, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy, and osteoporosis and other non-menopausal disease states treated with supplemental estrogen.

Formulations of the present disclosure containing solubilized estradiol may be used to treat or prevent atrophic vaginitis or vulvo-vaginal atrophy. In various embodiments, a capsule, for example a softgel capsule, may be applied in or around the vagina.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

## EXAMPLES

## Example 1

## Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation.

TABLE 1

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
Transcutol HP	141
Capmul PG8	31.2

\*Literature reference - Salole, E. G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

In further solubility studies, estradiol was soluble at at least 6 mg/gm Miglyol Transcutol in ratios of 81:19 to 95:5, in

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Miglyol;ethanol at 91:11, and in Miglyol:Capmul PG8 at 88:11, but not in Miglyol:Transcutol at 96:4, Miglyol:Labrasol at 70:30 to 80:20, or Miglyol:Capmul PG8 at 86:14.

## Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with Capmul PG8 and Capmul MCM by mixing estradiol with various solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 2. It can be seen from these results that mixtures containing Miglyol: Capmul PG8 at 50%; and also Capmul MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. Capmul PG8 mixed with Miglyol at the 15 and 30% level did not provide sufficient solubility.

TABLE 2

Ingredient	Solubility (mg/g)
Miglyol:Capmul PG8 (85:15)	4.40
Miglyol:Capmul PG8 (70:30)	8.60
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	>12
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	>12
Miglyol:Capmul PG8 (50:50)	14.0
Capmul MCM	19.8
Polysorbate 80:Capmul MCM (20:80)	15.0

## Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 3. Miglyol 812 with 4% Transcutol precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in Miglyol: Capmul blends at 30 and 50% or in Capmul MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 3

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Transcutol:Miglyol 812 (4:96)	4	Crystallizes after 96 hours
Miglyol 812:Capmul PG8 (70:30)	6	Clear, after 14 days
Miglyol 812:Capmul PG8 (50:50)	6	Clear, after 14 days
Transcutol:Miglyol 812:Capmul PG8 (5:80:15)	6	Clear, after 14 days
Capmul MCM	6	Clear after 14 days

12 mg estradiol solubilized in Miglyol:Capmul PG8 50:50, Capmul MCM, and in mixtures of Transcutol: Miglyol: Capmul PG8 are stable and do not precipitate for at least 12 days.

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TABLE 4

Formulation	Estradiol mg/g	Results Hot/Cold Cycling
Miglyol 812:Capmul PG8 (50:50)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Clear, after 12 days
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Clear, after 12 days
Capmul MCM	12	Clear after 12 days

## Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 5, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization, whereas the same concentration in Miglyol 812:Capmul PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and Capmul MCM are able to absorb a minimum of 7% water without recrystallization. All Capmul PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to Capmul PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 5

Formulation	Estradiol mg/g	Results after addition of 7% water
Miglyol 812:Capmul PG8 (75:25)	6	Precipitated
Miglyol 812:Capmul PG8 (50:50)	12	Hazy
Transcutol:Miglyol 812:Capmul PG8 (5:65:28)	12	Hazy
Capmul MCM	12	Clear
Transcutol:Miglyol 812:Capmul PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

## Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 6

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Mono-, di- or triglyceride (Miglyol 812)	qs
Diethylene Glycol Monoethylether (Transcutol HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

## Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 7

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 8

Ingredient	Mg/ Capsule	% w/w	Amount/ Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (Capmul MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to Capmul MCM and mixed until dissolved.

## Example 7

## Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. Miglyol was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, Miglyol may be used in embodiments comprising a suspension of progesterone, though Miglyol, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 9, the solubility of progesterone in Capmul MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. Miglyol had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or Capmul MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of Capmul MCM.



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TABLE 9

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM	73.4
Capmul PG8	95
Miglyol 812	27.8
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of Capmul MCM in combination with Gelucire 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a Capmul MCM and Gelucire 44/14 system, wherein the ratio of Capmul MCM to Gelucire 44/14 is 9:1.

TABLE 10

Ingredient	Progesterone Solubility (mg/g)
Capmul MCM:Gelucire 44/14 (9:1)	86.4
Capmul MCM:Gelucire 44/14 (7:3)	70.5
Capmul MCM:Gelucire 44/14 (6:4)	57.4

## Example 7-1

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 11

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
Capmul MCM, NF		82.57	577.97
Gelucire 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in TABLE 11 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N<sub>2</sub>. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, Capmul MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C. +/- 2° C. Gelucire 44/14 may be added to the Capmul MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the Gelucire 44/14 and the Capmul MCM.

Heat may be removed from the Gelucire 44/14 and Capmul MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone

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may then be added to the Gelucire 44/14, Capmul MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

## Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 12

Ingredient	mg/Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 13

Ingredient	Qty/Capsule (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/ diglycerides/ triglycerides of caprylic/capric acid (Capmul MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: Capmul MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

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TABLE 14

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (Gelucire 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 10

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279  $\mu$ m, an X75 of 7.442  $\mu$ m, and an X25 of 1.590  $\mu$ m. The Beckman Device also yielded that the mean particle size is 4.975  $\mu$ m, the median particle size is 4.279  $\mu$ m, the mode particle size is 6.453  $\mu$ m, and the standard deviation is 3.956  $\mu$ m. A graph of the particle distribution obtained is shown in FIG. 4.

## Example 11

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0  $\mu$ m, an X75 of 17.3  $\mu$ m, and an X25 of 5.3  $\mu$ m. The Beckman Device also yielded that the mean particle size is 11.8  $\mu$ m, the median particle size is 11.04  $\mu$ m, the mode particle size is 13.6  $\mu$ m, and the standard deviation is 7.8  $\mu$ m.

## Example 12

In order to increase the solubility of progesterone in the final solution, Gelucire 44/14 was added at about 10% w/w.

TABLE 15

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	Capmul MCM, NF		82.57	577.97	5.78
4.	Gelucire 44/14, NF		10.0	70.00	0.70
Total:			100.00	700.00	7.00

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An example of the final formulation is provided in Table 15. The manufacturing process is as follows. Capmul MCM is heated to 40° C. Gelucire 44/14 is heated to 65 C. and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

## Example 13

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 16

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	Capmul MCM, NF		73.371	146.74	1467.42
4.	Gelucire 44/14, NF		1.500	3.00	30.00
Total:			100.000	200.00 mg	2000.00

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 17

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	Capmul MCM, NF		65.32	391.93	3919.3
4.	Gelucire 44/14, NF		1.00	6.0	60.0
Total:			100.00	600.0 mg	6000.0

The manufacturing process is as follows. Capmul MCM is heated to 65° C. Gelucire 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation. Alternatively, Gelucire 44/14 is heated to 65 C. and Capmul MCM is heated to 40 C. +/-5 C. to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 40 C.; the mixture is then passed through a colloid mill, e.g., three times.

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Example 15

Study 352—Progesterone and Estradiol Combination Study Under Fed Conditions.

This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla.) (and 2.0 mg of ESTRACE® (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

Ingredient(s)	Amount (%) w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	7.14	50.00
Estradiol Hemihydrate, USP	0.30	2.07
Micronized Capmul MCM, NF, USP	83.27	582.93
Gelucire 44/14, NF	9.29	650
Total	100.00	700

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout

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the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of -70° C. ± 20° C. in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters C<sub>max</sub>, AUC<sub>0-t</sub> & AUC<sub>0-∞</sub> were calculated on data obtained from 24 subjects for the test product and reference product. In general, bio-availability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 18, below, for progesterone.

TABLE 18

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)				
Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
C <sub>max</sub>	47.0	43.0	81.0 ± 82.8	117.7 ± 173.7
AUC <sub>0-t</sub>	107.6	97.8	163.9 ± 136.5	191.1 ± 241.7
AUC <sub>0-∞</sub>	110.7	110.0	173.5 ± 143.0	207.1 ± 250.3

\*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study Under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the

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high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters  $C_{max}$ ,  $AUC_{0-t}$  &  $AUC_{0-\infty}$  were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 19, below for progesterone.

TABLE 19

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)				
Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean $\pm$ Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
$C_{max}$	2.3	3.0	$2.9 \pm 2.3$	$3.9 \pm 3.4$
$AUC_{0-t}$	8.4	10.9	$11.2 \pm 8.7$	$14.5 \pm 11.0$
$AUC_{0-\infty}$	12.9	17.2	$15.1 \pm 9.0$	$19.6 \pm 10.2$

\*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to Prometrium.

## Example 16

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material 100 is shown. Step 102 comprises heating an oily vehicle carrier to  $40^{\circ}\text{C} \pm 5^{\circ}\text{C}$ . Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, Capmul MCM.

Step 104 comprises mixing Gelucire 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 106 comprises mixing estradiol into the mixture of the oily vehicle and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 106 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ .

Step 108 comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step 110 comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and Gelucire 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 110 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Step 112 comprises degassing. The resulting mixture from step 112 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means.

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Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Heating may be performed until the temperature reaches  $80^{\circ}\text{C} \pm 5^{\circ}\text{C}$ .

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $\text{N}_2$ . Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to  $30^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of  $55^{\circ}\text{C} \pm 10^{\circ}\text{C}$ . The wedge temperature may be  $38^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . The drum cooling temperature may be  $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$ . The encapsulator may be lubricated using MIGLYOL 812 or other suitable lubricant. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness  $0.85\text{ mm} \pm 0.05\text{ mm}$  using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight  $\pm 5\%$  (i.e.,  $650 \pm 33\text{ mg}$  and  $325 \pm 16.3\text{ mg}$ ).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step 308 may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step 310 may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

## Example 17

Solubility of Estradiol in Soy Bean Oil, Peanut Oil, and Safflower Oil

Data was obtained visually by making the mixtures described below, sonicating the mixtures, and then seeing if a clear solution resulted. If a clear solution was achieved, it was an indication of solubility at the level studied.

Procedures and Results:

Step 1.

0.3% of Estradiol suspension in each oil was prepared by adding 30 mg Estradiol to solvent and QS to 10 g. Samples were mixed on vortex for 2 hours, heated @  $50^{\circ}\text{C}$ . for 30 minutes and then mixed for 1 hour more. All samples were still in suspension form.



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Step 2.

Each sample was diluted to 0.24% (by adding 2.5 g more oil) and mixed for 2 hours and heated @ 50° C. for 30 min and mixed again for one hour. All the samples were still cloudy. Samples were kept at room temperature overnight to see if they precipitate or if un-dissolved API settles out. After 20 hours at room temperature, it was observed that all samples still had un-dissolved API.

Step 3.

Each sample was diluted to 0.2% (by adding 2.5 g more oil) and mixed 2 for hours and heated @ 50° C. for 30 min and mixed again for one hour. All the samples were still slightly cloudy, indicating that the estradiol was not completely dissolved.

TABLE 20

Ingredient	Estradiol Solubility (mg/g)	Estradiol Solubility (% w/w)
Peanut Oil	<2	<0.2
Safflower Oil	<2	<0.2
Soy Bean Oil	<2	<0.2

The solubility of estradiol in all three oils was less than 2 mg/g (0.2% w/w). This level of solubility is significantly below the solubility that the present inventors have discovered can be achieved in other oils, e.g., medium chain fatty acid esters, such as the mono/diglycerides, propylene glycol esters, and polyethylene glycol esters discussed above.

In sum, if no heat is used to dissolve estradiol in safflower oil, it will not go into solution. Given that the estradiol did not dissolve at 50 C., oils such as safflower oil will not be useful in the methods of the invention using medium chain fatty acid esters as described hereinabove.

## Example 18

## Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of Prometrium and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37 C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from Prometrium. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from Prometrium is attached as FIG. 5.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present dis-

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closure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

We claim:

1. A pharmaceutical formulation for administering estradiol and progesterone to a mammal in need thereof, comprising

solubilized estradiol,  
solubilized progesterone,  
suspended progesterone, and  
an oil,

wherein each of the solubilized estradiol, the solubilized progesterone, and the suspended progesterone is present in the oil, and

wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids.

2. The pharmaceutical formulation of claim 1 wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, and wherein the medium chain fatty acid esters are predominantly esters of

C6 to C10 fatty acids.

3. The pharmaceutical formulation of claim 1 wherein the oil is predominantly mono- and diglycerides.

4. The pharmaceutical formulation of claim 1 wherein at least 90% of the total estradiol is solubilized.

5. The pharmaceutical formulation of claim 1 further comprising a surfactant.

6. The pharmaceutical formulation of claim 5 wherein the surfactant is a non-ionic surfactant.

7. The pharmaceutical formulation of claim 6 wherein the surfactant is lauroyl polyoxyl-32-glycerides.

8. The pharmaceutical formulation of claim 1 comprising: 30 to 35 wt % progesterone,  
0.1 to 0.4 wt % estradiol

55 to 75 wt % of the oil, wherein the oil is predominantly medium chain fatty acid mono- and diglycerides, and 0.5 to 10wt % non-ionic surfactant.

9. The pharmaceutical formulation of claim 8 further comprising gelatin, glycerol, and coloring agents.

10. The pharmaceutical formulation of claim 1 wherein the progesterone is released more rapidly than progesterone in peanut oil.

11. The pharmaceutical formulation of claim 1 wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, and wherein the medium chain fatty acid esters are predominantly esters of C8 to C12 fatty acids.

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12. The pharmaceutical formulation of claim 1 wherein the oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, and wherein the medium chain fatty acid esters are predominantly esters of C8 to C10 fatty acids.

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13. A method of treating at least one progesterone-deficient state in a mammal in need of treatment comprising administering an effective amount of a pharmaceutical formulation of claim 1.

14. A method of treating at least one estrogen-deficient state in a mammal in need of treatment comprising administering an effective amount of a pharmaceutical formulation of claim 1.

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\* \* \* \* \*

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UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 9,301,920 B2  
APPLICATION NO. : 13/843428  
DATED : April 5, 2016  
INVENTOR(S) : Brian A. Bernick et al.

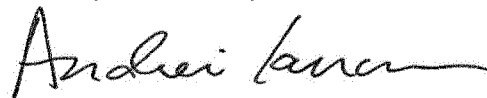
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

At item (72), please add inventor --Frederick D. Sancilio, Palm Beach Gardens, FL (US)--

Signed and Sealed this  
Twenty-sixth Day of March, 2019

A handwritten signature in black ink, appearing to read "Andrei Iancu".

Andrei Iancu  
*Director of the United States Patent and Trademark Office*

# EXHIBIT K



US010052386B2

(12) **United States Patent**  
**Bernick et al.**

(10) **Patent No.:** **US 10,052,386 B2**

(45) **Date of Patent:** **\*Aug. 21, 2018**

(54) **PROGESTERONE FORMULATIONS**

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(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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§ 371 (c)(1),

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**A61K 31/56** (2006.01)

**A61K 47/44** (2017.01)

**A61K 47/10** (2017.01)

**A61K 47/14** (2017.01)

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**A61K 31/565** (2006.01)

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**A61K 45/06** (2006.01)

**A61K 9/107** (2006.01)

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(58) **Field of Classification Search**

CPC ..... **A61K 31/57**; **A61K 47/44**; **A61K 47/10**  
See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

1,967,351	A	7/1934	Dolay
2,232,438	A	2/1941	Butenandt
2,379,832	A	7/1945	Serini et al.
2,649,399	A	8/1953	Beall et al.
3,198,707	A	8/1965	Nomine et al.
3,478,070	A	11/1969	Stein et al.
3,526,648	A	9/1970	Bertin et al.
3,710,795	A	1/1973	Higuchi et al.
3,729,560	A	4/1973	Hagerman
3,729,566	A	4/1973	Ericsson et al.
3,755,573	A	8/1973	Berman
3,755,575	A	8/1973	Lerner
3,903,880	A	9/1975	Higuchi et al.
3,916,898	A	11/1975	Robinson
3,916,899	A	11/1975	Theeuwes et al.
3,921,636	A	11/1975	Zaffaroni
3,923,997	A	12/1975	Meuly
3,948,254	A	4/1976	Zaffaroni
3,971,367	A	7/1976	Zaffaroni
3,977,404	A	8/1976	Theeuwes
3,993,072	A	11/1976	Zaffaroni

(Continued)

**FOREIGN PATENT DOCUMENTS**

BR	PI 1001367-9	A2	7/2012
CA	2548281	A1	6/2005

(Continued)

**OTHER PUBLICATIONS**

US 6,214,374, 04/2001, Schmirler et al. (withdrawn)  
Abbas, M.A., et al., "Regression of Endometrial Implants Treated with Vitamin D3 in a Rat Model of Endometriosis," European Journal of Pharmacology 715(1-3):72-75, Elsevier Science, Netherlands (2013).

Abitec Corporation Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2 pages (2013).  
Advisory Action dated Jan. 29, 2007 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.

Alvarez, P., et al., "Ectopic Uterine Tissue as a Chronic Pain Generator," Neuroscience 225:269-282, Elsevier Science, United States (2012).

(Continued)

Primary Examiner — Samira Jean-Louis

(74) Attorney, Agent, or Firm — Sterne Kessler Goldstein & Fox; Matthew Bodenstein

(57) **ABSTRACT**

Various pharmaceutical formulations are disclosed herein. For example, a pharmaceutical formulation is disclosed comprising ultra-micronized progesterone.

**40 Claims, 6 Drawing Sheets**

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

4,008,719 A	2/1977	Theeuwes et al.	5,620,705 A	4/1997	Dong et al.
4,012,496 A	3/1977	Schopflin et al.	5,626,866 A	5/1997	Ebert et al.
4,014,334 A	3/1977	Theeuwes et al.	5,629,021 A	5/1997	Wright
4,014,987 A	3/1977	Heller et al.	5,633,011 A	5/1997	Dong et al.
4,016,251 A	4/1977	Higuchi et al.	5,633,242 A	5/1997	Oettel et al.
4,071,623 A	1/1978	van der Vies	5,639,743 A	6/1997	Kaswan et al.
4,093,709 A	6/1978	Choi et al.	5,653,983 A	8/1997	Meybeck et al.
4,154,820 A	5/1979	Simoons	5,656,286 A	8/1997	Miranda et al.
4,155,991 A	5/1979	Schopflin et al.	5,660,839 A	8/1997	Allec et al.
4,196,188 A	4/1980	Besins	5,662,927 A	9/1997	Ehrlich et al.
4,215,691 A	8/1980	Wong	5,663,160 A	9/1997	Meybeck et al.
4,237,885 A	12/1980	Wong et al.	5,676,968 A	10/1997	Lipp et al.
4,310,510 A	1/1982	Sherman et al.	5,677,292 A	10/1997	Li et al.
4,327,725 A	5/1982	Cortese et al.	5,686,097 A	11/1997	Taskovich et al.
4,372,951 A	2/1983	Vorys	5,693,335 A	12/1997	Xia et al.
4,384,096 A	5/1983	Sonnabend	5,694,947 A	12/1997	Lehtinen et al.
4,393,871 A	7/1983	Vorhauer et al.	5,700,480 A	12/1997	Hille et al.
4,402,695 A	9/1983	Wong	5,709,844 A	1/1998	Arbeit et al.
4,423,151 A	12/1983	Baranczuk	5,719,197 A	2/1998	Kanios et al.
4,449,980 A	5/1984	Millar et al.	5,735,801 A	4/1998	Caillouette
4,610,687 A	9/1984	Fogwell	5,739,176 A	4/1998	Dunn et al.
4,629,449 A	12/1986	Wong	5,744,463 A	4/1998	Bar
4,732,763 A	3/1988	Beck et al.	5,747,058 A	5/1998	Tipton et al.
4,738,957 A	4/1988	Laurent et al.	5,762,614 A	6/1998	Caillouette
4,756,907 A	7/1988	Beck et al.	5,770,176 A	6/1998	Nargessi
4,762,717 A	8/1988	Crowley, Jr.	5,770,219 A	6/1998	Chiang et al.
4,788,062 A	11/1988	Gale et al.	5,770,220 A	6/1998	Meconi et al.
4,816,257 A	3/1989	Buster et al.	5,770,227 A	6/1998	Dong et al.
4,822,616 A	4/1989	Zimmermann et al.	5,776,495 A	7/1998	Duclos et al.
4,865,848 A	9/1989	Cheng et al.	5,780,044 A	7/1998	Yewey et al.
4,900,734 A	2/1990	Maxson et al.	5,780,050 A	7/1998	Jain et al.
4,906,475 A	3/1990	Kim	5,788,980 A	8/1998	Nabahi
4,942,158 A	7/1990	Sarpotdar et al.	5,788,984 A	8/1998	Guenther et al.
4,961,931 A	10/1990	Wong	5,789,442 A	8/1998	Garfield et al.
5,030,629 A	7/1991	Rajadhyaksha	5,811,416 A	9/1998	Chwalisz et al.
5,064,654 A	11/1991	Berner et al.	5,811,547 A	9/1998	Nakamichi et al.
5,108,995 A	4/1992	Casper	5,814,329 A	9/1998	Shah
5,128,138 A	7/1992	Blank	5,820,878 A	10/1998	Hirano et al.
5,130,137 A	7/1992	Crowley, Jr.	5,827,200 A	10/1998	Caillouette
5,140,021 A	8/1992	Maxson et al.	5,840,327 A	11/1998	Gale et al.
5,211,952 A	5/1993	Spicer et al.	5,843,468 A	12/1998	Burkoth et al.
5,252,334 A	10/1993	Chiang et al.	5,843,979 A	12/1998	Wille et al.
5,280,023 A	1/1994	Ehrlich et al.	5,858,394 A	1/1999	Lipp et al.
5,288,496 A	2/1994	Lewis	5,863,552 A	1/1999	Yue
5,340,584 A	8/1994	Spicer et al.	5,866,603 A	2/1999	Li et al.
5,340,585 A	8/1994	Pike et al.	5,882,676 A	3/1999	Lee et al.
5,340,586 A	8/1994	Pike et al.	5,885,612 A	3/1999	Meconi et al.
5,362,497 A	11/1994	Yamada et al.	5,888,533 A	3/1999	Dunn
5,382,573 A	1/1995	Casper	5,891,462 A	4/1999	Carrara
5,393,528 A	2/1995	Staab	5,891,868 A	4/1999	Cummings et al.
5,393,529 A	2/1995	Hoffmann et al.	5,898,038 A	4/1999	Yallampalli et al.
5,419,910 A	5/1995	Lewis	5,902,603 A	5/1999	Chen et al.
5,468,736 A	11/1995	Hodgen	5,904,931 A	5/1999	Lipp et al.
5,474,783 A	12/1995	Miranda et al.	5,906,830 A	5/1999	Farinas et al.
5,480,776 A	1/1996	Dullien	5,912,010 A	6/1999	Wille et al.
5,514,673 A	5/1996	Heckenmueller et al.	5,916,176 A	6/1999	Caillouette
5,516,528 A	5/1996	Hughes et al.	RE36,247 E	7/1999	Plunkett et al.
5,527,534 A	6/1996	Myhling	5,919,477 A	7/1999	Bevan et al.
5,529,782 A	6/1996	Staab	5,922,349 A	7/1999	Elliesen et al.
5,538,736 A	7/1996	Hoffmann et al.	5,928,666 A	7/1999	Farinas et al.
5,543,150 A	8/1996	Bologna et al.	5,942,243 A	8/1999	Shah
5,547,948 A	8/1996	Barcomb	5,952,000 A	9/1999	Venkateshwaran et al.
5,556,635 A	9/1996	Istin et al.	5,958,446 A	9/1999	Miranda et al.
5,565,199 A	10/1996	Page et al.	5,962,445 A	10/1999	Stewart
5,567,831 A	10/1996	Li	5,968,919 A	10/1999	Samour et al.
5,569,652 A	10/1996	Beier et al.	5,972,372 A	10/1999	Saleh et al.
5,580,572 A	12/1996	Mikler et al.	5,985,311 A	11/1999	Cordes et al.
5,582,592 A	12/1996	Kendrick	5,985,850 A	11/1999	Falk et al.
5,585,370 A	12/1996	Casper	5,985,861 A	11/1999	Levine et al.
5,595,759 A	1/1997	Wright et al.	5,989,568 A	11/1999	Breton et al.
5,595,970 A	1/1997	Garfield et al.	5,993,856 A	11/1999	Ragavan et al.
5,605,702 A	2/1997	Teillaud et al.	6,001,846 A	12/1999	Edwards et al.
5,607,691 A	3/1997	Hale et al.	6,007,835 A	12/1999	Bon-Lapillonne et al.
5,607,693 A	3/1997	Bonte et al.	6,010,715 A	1/2000	Wick et al.
5,609,617 A	3/1997	Shealy et al.	6,013,276 A	1/2000	Math et al.
			6,022,562 A	2/2000	Autant et al.
			6,024,974 A	2/2000	Li
			6,024,976 A	2/2000	Miranda et al.
			6,028,057 A	2/2000	Burns

## US 10,052,386 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

6,030,948	A	2/2000	Mann	6,451,779	B1	9/2002	Hesch
6,039,968	A	3/2000	Nabahi	6,455,246	B1	9/2002	Howett et al.
6,040,340	A	3/2000	Chwalisz et al.	6,455,517	B1	9/2002	Tanabe et al.
6,056,972	A	5/2000	Hermismeyer	6,465,004	B1	10/2002	Rossi-Montero et al.
6,060,077	A	5/2000	Meignant	6,465,005	B1	10/2002	Biali et al.
6,068,853	A	5/2000	Giannos et al.	6,465,006	B1	10/2002	Zhang et al.
6,074,625	A	6/2000	Hawthorne et al.	6,468,526	B2	10/2002	Chrisope
6,077,531	A	6/2000	Salin-Drouin	6,469,016	B1	10/2002	Place et al.
6,080,118	A	6/2000	Blythe	6,472,434	B1	10/2002	Place et al.
6,083,178	A	7/2000	Caillouette	6,479,232	B1	11/2002	Howett et al.
6,086,916	A	7/2000	Agnus et al.	6,495,160	B2	12/2002	Esposito et al.
6,087,352	A	7/2000	Trout	6,500,814	B1	12/2002	Hesch
6,090,404	A	7/2000	Meconi et al.	6,503,896	B1	1/2003	Tanabe et al.
6,096,338	A	8/2000	Lacy et al.	6,511,969	B1	1/2003	Hermismeyer
6,106,848	A	8/2000	Preuillh et al.	6,521,250	B2	2/2003	Meconi et al.
6,117,446	A	9/2000	Place	6,526,980	B1	3/2003	Tracy et al.
6,117,450	A	9/2000	Dittgen et al.	6,528,094	B1	3/2003	Savoir et al.
6,124,362	A	9/2000	Bradbury et al.	6,531,149	B1	3/2003	Kirstgen et al.
6,133,251	A	10/2000	Dittgen et al.	6,537,580	B1	3/2003	Savoir et al.
6,133,320	A	10/2000	Yallampalli et al.	6,538,039	B2	3/2003	Laurent
6,139,868	A	10/2000	Hoffmann	6,544,196	B2	4/2003	Caillouette
6,139,873	A	10/2000	Hughes, Jr. et al.	6,544,553	B1	4/2003	Hsia et al.
6,149,935	A	11/2000	Chiang et al.	6,548,053	B1	4/2003	Stewart et al.
6,153,216	A	11/2000	Cordes et al.	6,548,491	B2	4/2003	Tanabe et al.
6,165,491	A	12/2000	Grasset et al.	6,551,611	B2	4/2003	Elliesen et al.
6,165,975	A	12/2000	Adams et al.	6,555,131	B1	4/2003	Wolff et al.
6,187,323	B1	2/2001	Aiache et al.	6,562,367	B1	5/2003	Wolff et al.
6,187,339	B1	2/2001	de Haan et al.	6,562,370	B2	5/2003	Luo et al.
6,190,331	B1	2/2001	Caillouette	6,562,790	B2	5/2003	Chein et al.
6,201,072	B1	3/2001	Rathi et al.	6,569,463	B2	5/2003	Patel et al.
6,217,886	B1	4/2001	Önyüksel et al.	6,583,129	B1	6/2003	Mazer et al.
6,225,297	B1	5/2001	Stockemann et al.	6,586,006	B2	7/2003	Roser et al.
6,227,202	B1	5/2001	Matapurkar	6,589,549	B2	7/2003	Shin et al.
6,228,383	B1	5/2001	Hansen et al.	6,593,317	B1	7/2003	de Ziegler et al.
6,228,852	B1	5/2001	Shaak	6,599,519	B1	7/2003	Seo et al.
6,242,509	B1	6/2001	Berger et al.	6,610,652	B2	8/2003	Adams et al.
6,245,811	B1	6/2001	Horrobin et al.	6,610,670	B2	8/2003	Backensfeld et al.
6,262,115	B1	7/2001	Guittard et al.	6,610,674	B1	8/2003	Schreiber
6,264,980	B1	7/2001	Hille	6,635,274	B1	10/2003	Masiz et al.
6,267,984	B1	7/2001	Beste et al.	6,638,528	B1	10/2003	Kanios
6,274,165	B1	8/2001	Meconi et al.	6,638,536	B2	10/2003	Savoir et al.
6,277,418	B1	8/2001	Marakverich et al.	6,645,528	B1	11/2003	Straub et al.
6,283,927	B1	9/2001	Caillouette	6,649,155	B1	11/2003	Dunlop et al.
6,287,588	B1	9/2001	Shih et al.	6,653,298	B2	11/2003	Potter et al.
6,287,693	B1	9/2001	Savoir et al.	6,656,929	B1	12/2003	Agnus et al.
6,294,188	B1	9/2001	Ragavan et al.	6,660,726	B2	12/2003	Hill et al.
6,294,192	B1	9/2001	Patel et al.	6,663,608	B2	12/2003	Rathbone et al.
6,294,550	B1	9/2001	Place et al.	6,663,895	B2	12/2003	Savoir et al.
6,299,900	B1	10/2001	Reed et al.	6,682,757	B1	1/2004	Wright
6,303,132	B1	10/2001	Nelson	6,692,763	B1	2/2004	Cummings et al.
6,303,588	B1	10/2001	Danielov	6,708,822	B1	3/2004	Muni
6,306,841	B1	10/2001	Place et al.	6,720,001	B2	4/2004	Chen et al.
6,306,914	B1	10/2001	de Ziegler et al.	6,737,081	B2	5/2004	Savoir et al.
6,309,669	B1	10/2001	Setterstrom et al.	6,740,333	B2	5/2004	Beckett et al.
6,309,848	B1	10/2001	Howett et al.	6,743,448	B2	6/2004	Kryger
6,312,703	B1	11/2001	Orthofer	6,743,815	B2	6/2004	Huebner et al.
6,328,987	B1	12/2001	Marini	6,747,018	B2	6/2004	Tanabe et al.
6,342,491	B1	1/2002	Dey et al.	6,750,291	B2	6/2004	Kim et al.
6,344,211	B1	2/2002	Hille	6,756,208	B2	6/2004	Griffin et al.
6,372,209	B1	4/2002	Chrisope	6,776,164	B2	8/2004	Bunt et al.
6,372,245	B1	4/2002	Bowman et al.	6,787,152	B2	9/2004	Kirby et al.
6,372,246	B1	4/2002	Wei et al.	6,805,877	B2	10/2004	Massara et al.
6,387,390	B1	5/2002	Deaver et al.	6,809,085	B1	10/2004	Elson et al.
6,402,705	B1	6/2002	Caillouette	6,818,226	B2	11/2004	Reed et al.
6,416,778	B1	7/2002	Ragavan et al.	6,821,524	B2	11/2004	Marini
6,420,352	B1	7/2002	Knowles	6,841,716	B1	1/2005	Tsutsumi
6,423,039	B1	7/2002	Rathbone et al.	6,844,334	B2	1/2005	Hill et al.
6,423,683	B1	7/2002	Heaton et al.	6,855,703	B1	2/2005	Hill et al.
6,432,438	B1	8/2002	Shukla	6,860,859	B2	3/2005	Mehrotra et al.
6,436,633	B1	8/2002	Kreider et al.	6,866,865	B2	3/2005	Hsia et al.
6,440,454	B1	8/2002	Santoro et al.	6,869,969	B2	3/2005	Heubner et al.
6,444,224	B1	9/2002	Rathbone et al.	6,878,518	B2	4/2005	Whitehead
6,444,234	B1	9/2002	Kirby et al.	6,901,278	B1	5/2005	Notelovitz
6,451,300	B1	9/2002	Dunlop et al.	6,905,705	B2	6/2005	Palm et al.
6,451,339	B2	9/2002	Patel et al.	6,911,211	B2	6/2005	Eini et al.
				6,911,438	B2	6/2005	Wright
				6,923,988	B2	8/2005	Patel et al.
				6,924,274	B2	8/2005	Lardy et al.
				6,932,983	B1	8/2005	Straub et al.

## US 10,052,386 B2

Page 4

(56)

## References Cited

## U.S. PATENT DOCUMENTS

6,939,558 B2	9/2005	Massara et al.	7,732,408 B2	6/2010	Josephson et al.
6,943,021 B2	9/2005	Klausner et al.	7,749,989 B2	7/2010	Hill et al.
6,958,327 B1	10/2005	Hillisch et al.	7,767,656 B2	8/2010	Shoichet et al.
6,960,337 B2	11/2005	Daniels et al.	7,799,769 B2	9/2010	White et al.
6,962,691 B1	11/2005	Lulla et al.	7,815,936 B2	10/2010	Hasenzahl et al.
6,962,908 B2	11/2005	Aloba et al.	7,815,949 B2	10/2010	Cohen
6,967,194 B1	11/2005	Matsuo et al.	7,829,115 B2	11/2010	Besins et al.
6,974,569 B2	12/2005	Dunlop et al.	7,829,116 B2	11/2010	Griswold et al.
6,977,250 B2	12/2005	Rodriguez	RE42,012 E	12/2010	Deaver et al.
6,978,945 B2	12/2005	Wong et al.	7,850,992 B2	12/2010	Kim et al.
6,995,149 B1	2/2006	Endrikat et al.	7,854,753 B2	12/2010	Kraft et al.
7,004,321 B1	2/2006	Palm et al.	7,858,607 B2	12/2010	Mamchur
7,005,429 B2	2/2006	Dey et al.	RE42,072 E	1/2011	Deaver et al.
7,011,846 B2	3/2006	Shojaei et al.	7,862,552 B2	1/2011	McIntyre et al.
7,018,992 B2	3/2006	Koch et al.	7,867,990 B2	1/2011	Schultz et al.
7,030,104 B2	4/2006	Gray et al.	7,871,643 B2	1/2011	Lizio et al.
7,030,157 B2	4/2006	Ke et al.	7,879,830 B2	2/2011	Wiley
RE39,104 E	5/2006	Duclos et al.	7,884,093 B2	2/2011	Creasy et al.
7,074,779 B2	7/2006	Sui et al.	7,925,519 B2	4/2011	Greene
7,083,590 B1	8/2006	Bunt et al.	7,939,104 B2	5/2011	Barbera et al.
7,091,213 B2	8/2006	Metcalf, III et al.	7,943,602 B2	5/2011	Bunschoten et al.
7,094,228 B2	8/2006	Zhang et al.	7,943,604 B2	5/2011	Coelingh Bennink et al.
7,097,853 B1	8/2006	Garbe et al.	7,945,459 B2	5/2011	Grace et al.
7,101,342 B1	9/2006	Caillouette	7,960,368 B2	6/2011	Nickisch et al.
7,105,573 B2	9/2006	Krajcik et al.	7,989,436 B2	8/2011	Hill et al.
7,135,190 B2	11/2006	Piao et al.	7,989,487 B2	8/2011	Welsh et al.
7,153,522 B1	12/2006	Ikeura et al.	8,022,053 B2	9/2011	Mueller et al.
7,163,681 B2	1/2007	Giles-Komar et al.	8,048,017 B2	11/2011	Xu
7,163,699 B2	1/2007	Besse	8,048,869 B2	11/2011	Bunschoten et al.
7,175,850 B2	2/2007	Cevc	8,063,030 B2	11/2011	Ellman
7,179,799 B2	2/2007	Hill et al.	8,071,576 B2	12/2011	Coelingh Bennink et al.
7,196,074 B2	3/2007	Blye et al.	8,071,729 B2	12/2011	Giles-Komar et al.
7,198,800 B1	4/2007	Ko	8,075,916 B2	12/2011	Song et al.
7,198,801 B2	4/2007	Carrara et al.	8,075,917 B2	12/2011	Chung et al.
7,226,910 B2	6/2007	Wilson et al.	8,076,317 B2	12/2011	Kulmann
7,247,625 B2	7/2007	Zhang et al.	8,076,319 B2	12/2011	Leonard
7,250,446 B2	7/2007	Sangita et al.	8,080,553 B2	12/2011	Keith et al.
7,267,829 B2	9/2007	Kirby et al.	8,088,605 B2	1/2012	Beaudet et al.
7,300,926 B2	11/2007	Prokai et al.	8,096,940 B2	1/2012	Josephson et al.
7,303,763 B2	12/2007	Ho	8,101,209 B2	1/2012	Legrand et al.
7,317,037 B2	1/2008	Fensome et al.	8,101,773 B2	1/2012	Smith et al.
7,329,654 B2	2/2008	Kanojia et al.	8,114,152 B2	2/2012	Furst
7,335,650 B2	2/2008	Potter et al.	8,114,434 B2	2/2012	Sasaki et al.
7,374,779 B2	5/2008	Chen et al.	8,114,442 B2	2/2012	Tucker et al.
7,378,404 B2	5/2008	Peters et al.	8,119,741 B2	2/2012	Pavlin
7,381,427 B2	6/2008	Ancira et al.	8,121,886 B2	2/2012	Azar
7,388,006 B2	6/2008	Schmees et al.	8,124,118 B2	2/2012	Lennernas et al.
7,387,789 B2	7/2008	Klose et al.	8,124,595 B2	2/2012	Boissonneault
7,414,043 B2	8/2008	Kosemund et al.	8,147,561 B2	4/2012	Binmoeller
7,427,413 B2	9/2008	Savoir et al.	8,148,546 B2	4/2012	Schuster et al.
7,427,609 B2	9/2008	Leonard	8,158,613 B2	4/2012	Staniforth et al.
7,429,576 B2	9/2008	Labrie	8,158,614 B2	4/2012	Lambert et al.
7,431,941 B2	10/2008	Besins et al.	8,163,722 B2	4/2012	Savoir et al.
7,456,159 B2	11/2008	Houze et al.	8,177,449 B2	5/2012	Bayly et al.
7,459,445 B2	12/2008	Hill et al.	8,182,833 B2	5/2012	Hermesmyer
7,465,587 B2	12/2008	Imrich	8,187,615 B2	5/2012	Friedman
7,470,433 B2	12/2008	Carrara et al.	8,195,403 B2	6/2012	Ishikawa et al.
7,485,666 B2	2/2009	Villanueva et al.	8,202,736 B2	6/2012	Mousa et al.
7,497,855 B2	3/2009	Ausiello et al.	8,217,024 B2	7/2012	Ahmed et al.
7,498,303 B2	3/2009	Arnold et al.	8,221,785 B2	7/2012	Chien
7,534,765 B2	5/2009	Gregg et al.	8,222,008 B2	7/2012	Thoene
7,534,780 B2	5/2009	Wyrwa et al.	8,222,237 B2	7/2012	Nickisch et al.
7,550,142 B2	6/2009	Giles-Komar et al.	8,227,454 B2	7/2012	Hill et al.
7,563,565 B1	7/2009	Matsuo et al.	8,227,509 B2	7/2012	Castro et al.
7,569,274 B2	8/2009	Besse et al.	8,241,664 B2	8/2012	Dudley et al.
7,572,779 B2	8/2009	Aloba et al.	8,247,393 B2	8/2012	Ahmed et al.
7,572,780 B2	8/2009	Hermesmyer	8,257,724 B2	9/2012	Cromack et al.
7,589,082 B2	9/2009	Savoir et al.	8,257,725 B2	9/2012	Cromack et al.
7,671,027 B2	3/2010	Loumaye	8,268,352 B2	9/2012	Vaya et al.
7,674,783 B2	3/2010	Hermesmyer	8,268,806 B2	9/2012	Labrie
7,687,281 B2	3/2010	Roth et al.	8,268,878 B2	9/2012	Armer et al.
7,687,485 B2	3/2010	Levinson et al.	8,273,730 B2	9/2012	Fernandez et al.
7,694,683 B2	4/2010	Callister et al.	8,287,888 B2	10/2012	Song et al.
7,704,983 B1	4/2010	Hodgen et al.	8,288,366 B2	10/2012	Chochinov et al.
7,727,720 B2	6/2010	Dhallan	8,318,898 B2	11/2012	Fasel et al.
			8,324,193 B2	12/2012	Lee-Sepsick et al.
			8,329,680 B2	12/2012	Evans et al.
			8,337,814 B2	12/2012	Osbakken et al.
			8,344,007 B2	1/2013	Tang et al.



## US 10,052,386 B2

Page 5

(56)

## References Cited

## U.S. PATENT DOCUMENTS

8,349,820 B2	1/2013	Zeun et al.	2001/0005728 A1	6/2001	Guittard et al.
8,353,863 B2	1/2013	Imran	2001/0009673 A1	7/2001	Lipp et al.
8,357,723 B2	1/2013	Satyam	2001/0021816 A1	9/2001	Caillouette
8,361,995 B2	1/2013	Schramm	2001/0023261 A1	9/2001	Ryoo et al.
8,362,091 B2	1/2013	Tamarkin et al.	2001/0027189 A1	10/2001	Bennink et al.
8,372,424 B2	2/2013	Berry et al.	2001/0029357 A1	10/2001	Bunt et al.
8,372,806 B2	2/2013	Bohler et al.	2001/0031747 A1	10/2001	deZiegler et al.
8,377,482 B2	2/2013	Laurie et al.	2001/0032125 A1	10/2001	Bhan et al.
8,377,994 B2	2/2013	Gray et al.	2001/0034340 A1	10/2001	Pickar
8,394,759 B2	3/2013	Barathur et al.	2001/0053383 A1	12/2001	Miranda et al.
8,435,561 B2	3/2013	Besins et al.	2001/0056068 A1	12/2001	Chwalisz et al.
8,415,332 B2	4/2013	Diliberti et al.	2002/0012710 A1	1/2002	Lansky
8,420,111 B2	4/2013	Hermesmeyer	2002/0026158 A1	2/2002	Rathbone et al.
8,435,972 B2	5/2013	Stein et al.	2002/0028788 A1	3/2002	Bunt et al.
8,449,879 B2	5/2013	Laurent-Applegate et al.	2002/0035070 A1	3/2002	Gardlik et al.
8,450,108 B2	5/2013	Boyce	2002/0058648 A1	5/2002	Hammerly
8,454,945 B2	6/2013	McCook et al.	2002/0058926 A1	5/2002	Rathbone et al.
8,455,468 B2	6/2013	Hoffman et al.	2002/0064541 A1	5/2002	Lapidot et al.
8,461,138 B2	6/2013	Boissonneault	2002/0076441 A1	6/2002	Shin et al.
8,476,252 B2	7/2013	Achleitner et al.	2002/0102308 A1	8/2002	Wei et al.
8,481,488 B2	7/2013	Carter	2002/0107230 A1	8/2002	Waldon et al.
8,486,374 B2	7/2013	Tamarkin et al.	2002/0114803 A1	8/2002	Deaver et al.
8,486,442 B2	7/2013	Matsushita et al.	2002/0119174 A1	8/2002	Gardlik et al.
8,492,368 B2	7/2013	Vanlandingham et al.	2002/0119198 A1	8/2002	Gao et al.
8,507,467 B2	8/2013	Matsui et al.	2002/0132801 A1	9/2002	Heil et al.
8,512,693 B2	8/2013	Capito et al.	2002/0137749 A1	9/2002	Levinson et al.
8,512,754 B2	8/2013	Needham	2002/0142017 A1	10/2002	Simonnet
8,518,376 B2	8/2013	Tamarkin et al.	2002/0151530 A1	10/2002	Leonard et al.
8,536,159 B2	9/2013	Li et al.	2002/0156394 A1	10/2002	Mehrotra et al.
8,540,967 B2	9/2013	Barrett et al.	2002/0169150 A1	11/2002	Pickar
8,541,400 B2	9/2013	Johnsson et al.	2002/0169205 A1	11/2002	Chwalisz et al.
8,551,462 B2	10/2013	Goldstein et al.	2002/0173510 A1	11/2002	Levinson et al.
8,557,281 B2	10/2013	Halliday et al.	2002/0193356 A1	12/2002	Van Beek et al.
8,568,374 B2	10/2013	De Graaff et al.	2002/0193758 A1	12/2002	Sandberg
8,591,951 B2	11/2013	Kohn et al.	2002/0197286 A1	12/2002	Brandman et al.
8,613,951 B2	12/2013	Zale et al.	2003/0003139 A1	1/2003	Lipp et al.
8,633,178 B2	1/2014	Bernick et al.	2003/0004145 A1	1/2003	Leonard
8,633,180 B2	1/2014	Li et al.	2003/0007994 A1	1/2003	Bunt et al.
8,636,787 B2	1/2014	Sabaria	2003/0027772 A1	2/2003	Breton
8,636,982 B2	1/2014	Tamarkin et al.	2003/0044453 A1	3/2003	Dittgen et al.
8,653,129 B2	2/2014	Fein et al.	2003/0049307 A1	3/2003	Gyurik
8,658,627 B2	2/2014	Voskuhl	2003/0064097 A1	4/2003	Patel et al.
8,658,628 B2	2/2014	Baucom	2003/0064975 A1	4/2003	Koch et al.
8,663,681 B2	3/2014	Nakamichi et al.	2003/0072760 A1	4/2003	Sirbasku
8,663,692 B1	3/2014	Mueller et al.	2003/0073248 A1	4/2003	Roth et al.
8,663,703 B2	3/2014	Lerner et al.	2003/0073673 A1	4/2003	Hesch
8,664,207 B2	3/2014	Li et al.	2003/0077297 A1	4/2003	Chen et al.
8,669,293 B2	3/2014	Levy et al.	2003/0078245 A1	4/2003	Bennink et al.
8,679,552 B2	3/2014	Guthery	2003/0091620 A1	5/2003	Fikstad et al.
8,694,358 B2	4/2014	Tryfon	2003/0091640 A1	5/2003	Ramanathan et al.
8,697,127 B2	4/2014	Sah	2003/0092691 A1	5/2003	Besse et al.
8,697,710 B2	4/2014	Li et al.	2003/0096012 A1	5/2003	Besse et al.
8,703,105 B2	4/2014	Tamarkin et al.	2003/0104048 A1	6/2003	Patel et al.
8,709,385 B2	4/2014	Tamarkin et al.	2003/0109507 A1	6/2003	Franke et al.
8,709,451 B2	4/2014	Rapoport et al.	2003/0113268 A1	6/2003	Buenafoe et al.
8,715,735 B2	5/2014	Funke et al.	2003/0114420 A1	6/2003	Salvati et al.
8,721,331 B2	5/2014	Raghuprasad	2003/0114430 A1	6/2003	MacLeod et al.
8,722,021 B2	5/2014	Friedman et al.	2003/0124182 A1	7/2003	Shojaei et al.
8,734,846 B2	5/2014	Ali et al.	2003/0124191 A1	7/2003	Besse et al.
8,735,381 B2	5/2014	Podolski	2003/0130558 A1	7/2003	Massara et al.
8,741,336 B2	6/2014	Dipierro et al.	2003/0144258 A1	7/2003	Heil et al.
8,741,373 B2	6/2014	Bromley et al.	2003/0157157 A1	8/2003	Luo et al.
8,753,661 B2	6/2014	Steinmuller-Nethl et al.	2003/0166509 A1	9/2003	Edwards et al.
8,784,882 B2	7/2014	Mattern	2003/0170295 A1	9/2003	Kim et al.
8,815,261 B2	8/2014	Hanma	2003/0175329 A1	9/2003	Azarnoff et al.
8,846,648 B2	9/2014	Bernick et al.	2003/0175333 A1	9/2003	Shefer et al.
8,846,649 B2	9/2014	Bernick et al.	2003/0180352 A1	9/2003	Patel et al.
8,933,059 B2	1/2015	Bernick et al.	2003/0181353 A1	9/2003	Nyce
8,987,237 B2	3/2015	Bernick et al.	2003/0181728 A1	9/2003	Salvati et al.
8,987,238 B2	3/2015	Bernick et al.	2003/0191096 A1	10/2003	Leonard et al.
8,993,548 B2	3/2015	Bernick et al.	2003/0195177 A1	10/2003	Leonard et al.
8,993,549 B2	3/2015	Bernick et al.	2003/0215496 A1	11/2003	Patel et al.
9,006,222 B2	4/2015	Bernick et al.	2003/0219402 A1	11/2003	Rutter
9,012,434 B2	4/2015	Bernick et al.	2003/0220297 A1	11/2003	Berstein et al.
9,289,382 B2	3/2016	Bernick et al.	2003/0224057 A1	12/2003	Martin-Letellier et al.
			2003/0224059 A1	12/2003	Lerner et al.
			2003/0225047 A1	12/2003	Caubel et al.
			2003/0225048 A1	12/2003	Caubel et al.
			2003/0225050 A1	12/2003	Eichardt et al.

## US 10,052,386 B2

Page 6

(56)	References Cited			2005/0192253	A1	9/2005	Salvati et al.
	U.S. PATENT DOCUMENTS			2005/0192310	A1	9/2005	Gavai et al.
				2005/0196434	A1	9/2005	Brierre
				2005/0207990	A1	9/2005	Funke et al.
2003/0228686	A1	12/2003	Klausner et al.	2005/0209209	A1	9/2005	Koch et al.
2003/0229057	A1	12/2003	Caubel et al.	2005/0214384	A1	9/2005	Juturu et al.
2003/0235596	A1	12/2003	Gao et al.	2005/0220825	A1	10/2005	Funke et al.
2003/0236236	A1	12/2003	Chen et al.	2005/0220900	A1	10/2005	Popp et al.
2004/0009960	A1	1/2004	Heil et al.	2005/0222106	A1	10/2005	Bracht
2004/0022820	A1	2/2004	Anderson	2005/0228692	A1	10/2005	Hodgdon
2004/0034001	A1	2/2004	Karara	2005/0228718	A1	10/2005	Austin
2004/0037881	A1	2/2004	Guittard et al.	2005/0239747	A1	10/2005	Yang et al.
2004/0039356	A1	2/2004	Maki et al.	2005/0239758	A1	10/2005	Roby
2004/0043043	A1	3/2004	Schlyter et al.	2005/0244360	A1	11/2005	Billoni
2004/0043943	A1	3/2004	Guittard et al.	2005/0244522	A1	11/2005	Carrara et al.
2004/0044080	A1	3/2004	Place et al.	2005/0245902	A1	11/2005	Cornish et al.
2004/0048900	A1	3/2004	Flood	2005/0250746	A1	11/2005	Iammatteo
2004/0052824	A1	3/2004	Abou Chacra-Vernet et al.	2005/0250750	A1	11/2005	Cummings et al.
2004/0073024	A1	4/2004	Metcalf, III et al.	2005/0250753	A1	11/2005	Fink et al.
2004/0077605	A1	4/2004	Salvati et al.	2005/0256028	A1	11/2005	Yun et al.
2004/0077606	A1	4/2004	Salvati et al.	2005/0266078	A1	12/2005	Jorda et al.
2004/0087548	A1	5/2004	Salvati et al.	2005/0266088	A1	12/2005	Hinrichs et al.
2004/0087564	A1	5/2004	Wright et al.	2005/0271597	A1	12/2005	Keith
2004/0089308	A1	5/2004	Welch	2005/0271598	A1	12/2005	Friedman et al.
2004/0092494	A9	5/2004	Dudley	2005/0272685	A1	12/2005	Hung
2004/0092583	A1	5/2004	Shanahan-Prendergast	2005/0272712	A1	12/2005	Grubb et al.
2004/0093261	A1	5/2004	Jain et al.	2006/0009428	A1	1/2006	Grubb et al.
2004/0097468	A1	5/2004	Wimalawansa	2006/0014728	A1	1/2006	Chwalisz et al.
2004/0101557	A1	5/2004	Gibson et al.	2006/0018937	A1	1/2006	Friedman et al.
2004/0106542	A1	6/2004	Deaver et al.	2006/0019978	A1	1/2006	Balog
2004/0110732	A1	6/2004	Masini-Eteve et al.	2006/0020002	A1	1/2006	Salvati et al.
2004/0131670	A1	7/2004	Gao	2006/0030615	A1	2/2006	Fensome et al.
2004/0138103	A1	7/2004	Patt	2006/0034889	A1	2/2006	Jo et al.
2004/0142012	A1	7/2004	Bunt et al.	2006/0034904	A1	2/2006	Weimann
2004/0146539	A1	7/2004	Gupta	2006/0051391	A1	3/2006	Dvoskin et al.
2004/0146894	A1	7/2004	Warrington et al.	2006/0052341	A1	3/2006	Cornish et al.
2004/0161435	A1	8/2004	Gupta	2006/0069031	A1	3/2006	Loumaye
2004/0176324	A1	9/2004	Salvati et al.	2006/0078618	A1	4/2006	Constantinides et al.
2004/0176336	A1	9/2004	Rodriguez	2006/0083778	A1	4/2006	Allison et al.
2004/0185104	A1	9/2004	Piao et al.	2006/0084704	A1	4/2006	Shih et al.
2004/0191207	A1	9/2004	Lipari et al.	2006/0088580	A1	4/2006	Meconi et al.
2004/0191276	A1	9/2004	Muni	2006/0089337	A1	4/2006	Casper et al.
2004/0198706	A1	10/2004	Carrara et al.	2006/0093678	A1	5/2006	Chickering, III et al.
2004/0210280	A1	10/2004	Liedtke	2006/0100180	A1	5/2006	Nubbemeyer et al.
2004/0213744	A1	10/2004	Lulla et al.	2006/0106004	A1	5/2006	Brody et al.
2004/0219124	A1	11/2004	Gupta	2006/0110415	A1	5/2006	Gupta
2004/0225140	A1	11/2004	Fernandez et al.	2006/0111424	A1	5/2006	Salvati et al.
2004/0234606	A1	11/2004	Levine et al.	2006/0121102	A1	6/2006	Chiang
2004/0241219	A1	12/2004	Hille et al.	2006/0121626	A1	6/2006	Imrich
2004/0243437	A1	12/2004	Grace et al.	2006/0134188	A1	6/2006	Podhaisky et al.
2004/0253319	A1	12/2004	Netke et al.	2006/0135619	A1	6/2006	Kick et al.
2004/0259817	A1	12/2004	Waldon et al.	2006/0165744	A1	7/2006	Jamil et al.
2004/0266745	A1	12/2004	Schwanitz et al.	2006/0193789	A1	8/2006	Tamarkin et al.
2005/0003003	A1	1/2005	Basu et al.	2006/0194775	A1	8/2006	Tofovic et al.
2005/0004088	A1	1/2005	Hesch	2006/0204557	A1	9/2006	Gupta et al.
2005/0009800	A1	1/2005	Thumbbeck et al.	2006/0233743	A1	10/2006	Kelly
2005/0014729	A1	1/2005	Pulaski	2006/0233841	A1	10/2006	Brodbeck et al.
2005/0020550	A1	1/2005	Morris et al.	2006/0235037	A1	10/2006	Purandare et al.
2005/0020552	A1	1/2005	Aschkenasay et al.	2006/0240111	A1	10/2006	Fernandez et al.
2005/0021009	A1	1/2005	Massara et al.	2006/0246122	A1	11/2006	Langguth et al.
2005/0025833	A1	2/2005	Aschkenasay et al.	2006/0247216	A1	11/2006	Haj-Yehia
2005/0031651	A1	2/2005	Gervais et al.	2006/0247221	A1	11/2006	Coelingh Bennink et al.
2005/0042173	A1	2/2005	Besse et al.	2006/0251581	A1	11/2006	McIntyre et al.
2005/0042268	A1	2/2005	Aschkenasay et al.	2006/0252049	A1	11/2006	Shuler et al.
2005/0048116	A1	3/2005	Straub et al.	2006/0257472	A1	11/2006	Neilsen
2005/0054991	A1	3/2005	Tobyn et al.	2006/0275218	A1	12/2006	Tamarkin et al.
2005/0079138	A1	4/2005	Chickering, III et al.	2006/0275360	A1	12/2006	Ahmed et al.
2005/0085453	A1	4/2005	Govindarajan	2006/0276414	A1	12/2006	Coelingh Bennink et al.
2005/0101579	A1	5/2005	Shippen	2006/0280771	A1	12/2006	Groenewegen et al.
2005/0113350	A1	5/2005	Duesterberg et al.	2006/0280797	A1	12/2006	Shoichet et al.
2005/0118244	A1	6/2005	Theobald et al.	2006/0280800	A1	12/2006	Nagi et al.
2005/0118272	A1	6/2005	Besse et al.	2006/0292223	A1	12/2006	Woolfson et al.
2005/0129756	A1	6/2005	Podhaisky et al.	2007/0004693	A1	1/2007	Woolfson et al.
2005/0152956	A1	7/2005	Dudley	2007/0004694	A1	1/2007	Woolfson et al.
2005/0153946	A1	7/2005	Hirsh et al.	2007/0009559	A1	1/2007	Li et al.
2005/0164977	A1	7/2005	Coelingh Bennink	2007/0009594	A1	1/2007	Grubb et al.
2005/0182105	A1	8/2005	Nirschl et al.	2007/0010550	A1	1/2007	McKenzie
2005/0186141	A1	8/2005	Gonda et al.	2007/0014839	A1	1/2007	Bracht
2005/0187267	A1	8/2005	Hamann et al.	2007/0015698	A1	1/2007	Kleinman et al.

## US 10,052,386 B2

Page 7

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2007/0021360 A1	1/2007	Nyce et al.	2008/0220069 A1	9/2008	Allison
2007/0027201 A1	2/2007	McComas et al.	2008/0226698 A1	9/2008	Tang et al.
2007/0031491 A1	2/2007	Levine et al.	2008/0227763 A1	9/2008	Lanquetin et al.
2007/0037780 A1	2/2007	Ebert et al.	2008/0234199 A1	9/2008	Katamreddy
2007/0037782 A1	2/2007	Hibino et al.	2008/0234240 A1	9/2008	Duesterberg et al.
2007/0042038 A1	2/2007	Besse	2008/0255078 A1	10/2008	Katamreddy
2007/0060589 A1	3/2007	Purandare et al.	2008/0255089 A1	10/2008	Katamreddy
2007/0066628 A1	3/2007	Zhang et al.	2008/0261931 A1	10/2008	Hedner et al.
2007/0066637 A1	3/2007	Zhang et al.	2008/0299220 A1	12/2008	Tamarkin et al.
2007/0066675 A1	3/2007	Zhang et al.	2008/0306036 A1	12/2008	Katamreddy
2007/0078091 A1	4/2007	Hubler et al.	2008/0312197 A1	12/2008	Rodriguez
2007/0088029 A1	4/2007	Balog et al.	2008/0312198 A1	12/2008	Rodriguez
2007/0093548 A1	4/2007	Diffendal et al.	2008/0319078 A1	12/2008	Katamreddy
2007/0116729 A1	5/2007	Palepu	2009/0004246 A1	1/2009	Woolfson et al.
2007/0116829 A1	5/2007	Prakash et al.	2009/0010968 A1	1/2009	Allart et al.
2007/0128263 A1	6/2007	Gargiulo et al.	2009/0011041 A1	1/2009	Musaeva et al.
2007/0154533 A1	7/2007	Dudley	2009/0017120 A1	1/2009	Trimble et al.
2007/0167418 A1	7/2007	Ferguson	2009/0022683 A1	1/2009	Song et al.
2007/0178166 A1	8/2007	Bernstein et al.	2009/0047357 A1	2/2009	Tomohira et al.
2007/0184558 A1	8/2007	Roth et al.	2009/0053294 A1	2/2009	Prendergast
2007/0185068 A1	8/2007	Ferguson et al.	2009/0060982 A1	3/2009	Ron et al.
2007/0190022 A1	8/2007	Bacopoulos et al.	2009/0060997 A1	3/2009	Seitz et al.
2007/0191319 A1	8/2007	Ke et al.	2009/0068118 A1	3/2009	Eini et al.
2007/0196415 A1	8/2007	Chen et al.	2009/0074859 A1	3/2009	Patel
2007/0196433 A1	8/2007	Ron et al.	2009/0081206 A1	3/2009	Leibovitz
2007/0207225 A1	9/2007	Squadrito	2009/0081278 A1	3/2009	De Graaff et al.
2007/0225281 A1	9/2007	Zhang et al.	2009/0081303 A1	3/2009	Savoir et al.
2007/0232574 A1	10/2007	Galey et al.	2009/0092656 A1	4/2009	Klamerus et al.
2007/0238713 A1	10/2007	Gast et al.	2009/0093440 A1	4/2009	Murad
2007/0243229 A1	10/2007	Smith et al.	2009/0098069 A1	4/2009	Vacca
2007/0248658 A1	10/2007	Zurdo Schroeder et al.	2009/0099106 A1	4/2009	Phiasivongsa et al.
2007/0254858 A1	11/2007	Cronk	2009/0099149 A1	4/2009	Liu et al.
2007/0255197 A1	11/2007	Humberstone et al.	2009/0130029 A1	5/2009	Tamarkin et al.
2007/0264309 A1	11/2007	Chollet et al.	2009/0131385 A1	5/2009	Voskuhl
2007/0264345 A1	11/2007	Eros et al.	2009/0137478 A1	5/2009	Bernstein et al.
2007/0264349 A1	11/2007	Lee et al.	2009/0137538 A1	5/2009	Klamerus et al.
2007/0286819 A1	12/2007	DeVries et al.	2009/0143344 A1	6/2009	Chang
2007/0287688 A1	12/2007	Chan et al.	2009/0164341 A1	6/2009	Sunvold et al.
2007/0287789 A1	12/2007	Jones et al.	2009/0175799 A1	7/2009	Tamarkin et al.
2007/0292359 A1	12/2007	Friedman et al.	2009/0181088 A1	7/2009	Song et al.
2007/0292387 A1	12/2007	Jon et al.	2009/0186081 A1	7/2009	Holm et al.
2007/0292461 A1	12/2007	Tamarkin et al.	2009/0197843 A1	8/2009	Notelovitz et al.
2007/0292493 A1	12/2007	Brierre	2009/0203658 A1	8/2009	Marx et al.
2007/0298089 A1	12/2007	Saeki et al.	2009/0214474 A1	8/2009	Jennings
2008/0026035 A1	1/2008	Chollet et al.	2009/0227025 A1	9/2009	Nichols et al.
2008/0026040 A1	1/2008	Farr et al.	2009/0227550 A1	9/2009	Mattern
2008/0026062 A1	1/2008	Farr et al.	2009/0232897 A1	9/2009	Sahoo et al.
2008/0038219 A1	2/2008	Mosbaugh et al.	2009/0258096 A1	10/2009	Cohen
2008/0038350 A1	2/2008	Gerecke et al.	2009/0264395 A1	10/2009	Creasy
2008/0039405 A1	2/2008	Langley et al.	2009/0269403 A1	10/2009	Shaked et al.
2008/0050317 A1	2/2008	Tamarkin et al.	2009/0285772 A1	11/2009	Phiasivongsa et al.
2008/0051351 A1	2/2008	Ghisalberti	2009/0285869 A1	11/2009	Trimble
2008/0063607 A1	3/2008	Tamarkin et al.	2009/0318558 A1	12/2009	Kim et al.
2008/0069779 A1	3/2008	Tamarkin et al.	2009/0324714 A1	12/2009	Liu et al.
2008/0069791 A1	3/2008	Beissert	2009/0325916 A1	12/2009	Zhang et al.
2008/0085877 A1	4/2008	Bortz	2010/0008985 A1	1/2010	Pellikaan et al.
2008/0095831 A1	4/2008	McGraw	2010/0028360 A1	2/2010	Atwood
2008/0095838 A1	4/2008	Abou Chacra-Vernet	2010/0034838 A1	2/2010	Staniforth et al.
2008/0113953 A1	5/2008	De Vries et al.	2010/0034880 A1	2/2010	Sintov et al.
2008/0114050 A1	5/2008	Fensome et al.	2010/0040671 A1	2/2010	Ahmed et al.
2008/0119537 A1	5/2008	Zhang et al.	2010/0048523 A1	2/2010	Bachman et al.
2008/0125402 A1	5/2008	Dilberti	2010/0055138 A1	3/2010	Margulies et al.
2008/0138379 A1	6/2008	Jennings-Spring	2010/0074959 A1	3/2010	Hansom et al.
2008/0138390 A1	6/2008	Hsu et al.	2010/0086501 A1	4/2010	Chang et al.
2008/0139392 A1	6/2008	Acosta-Zara et al.	2010/0086599 A1	4/2010	Huempel et al.
2008/0145423 A1	6/2008	Khan et al.	2010/0092568 A1	4/2010	Lerner et al.
2008/0153789 A1	6/2008	Dmowski et al.	2010/0105071 A1	4/2010	Laufer et al.
2008/0175814 A1	7/2008	Phiasivongsa et al.	2010/0119585 A1	5/2010	Hille et al.
2008/0175905 A1	7/2008	Liu et al.	2010/0129320 A1	5/2010	Phiasivongsa et al.
2008/0175908 A1	7/2008	Liu et al.	2010/0136105 A1	6/2010	Chen et al.
2008/0188829 A1	8/2008	Creasy	2010/0137265 A1	6/2010	Leonard
2008/0206156 A1	8/2008	Cronk	2010/0137271 A1	6/2010	Chen et al.
2008/0206159 A1	8/2008	Tamarkin et al.	2010/0143420 A1	6/2010	Shenoy et al.
2008/0206161 A1	8/2008	Tamarkin et al.	2010/0143481 A1	6/2010	Shenoy et al.
2008/0214512 A1	9/2008	Seitz et al.	2010/0150993 A1	6/2010	Theobald et al.
			2010/0152144 A1	6/2010	Hermesmyer
			2010/0168228 A1	7/2010	Bose et al.
			2010/0183723 A1	7/2010	Laurent-Applegate et al.
			2010/0184736 A1	7/2010	Coelingh Bennink et al.

## US 10,052,386 B2

Page 8

(56)	<b>References Cited</b>				
	U.S. PATENT DOCUMENTS				
2010/0190758 A1	7/2010	Fausser et al.	2012/0046518 A1	2/2012	Yoakum et al.
2010/0204326 A1	8/2010	D'Souza	2012/0052077 A1	3/2012	Truitt, III et al.
2010/0210994 A1	8/2010	Zarif	2012/0058171 A1	3/2012	De Graaff et al.
2010/0221195 A1	9/2010	Tamarkin et al.	2012/0058962 A1	3/2012	Cumming et al.
2010/0227797 A1	9/2010	Axelsson et al.	2012/0058979 A1	3/2012	Keith et al.
2010/0240626 A1	9/2010	Kulkarni et al.	2012/0064135 A1	3/2012	Levin et al.
2010/0247482 A1	9/2010	Cui et al.	2012/0065179 A1	3/2012	Andersson
2010/0247632 A1	9/2010	Dong et al.	2012/0065221 A1	3/2012	Babul
2010/0247635 A1	9/2010	Rosenberg et al.	2012/0087872 A1	4/2012	Tamarkin et al.
2010/0255085 A1	10/2010	Liu et al.	2012/0101073 A1	4/2012	Mannion et al.
2010/0273730 A1	10/2010	Hsu et al.	2012/0121517 A1	5/2012	Song et al.
2010/0278759 A1	11/2010	Murad	2012/0121692 A1	5/2012	Xu et al.
2010/0279988 A1	11/2010	Setiawan et al.	2012/0122829 A1	5/2012	Taravella et al.
2010/0291191 A1	11/2010	Shoichet et al.	2012/0128625 A1	5/2012	Shalwitz et al.
2010/0292199 A1	11/2010	Leverd et al.	2012/0128654 A1	5/2012	Terpstra et al.
2010/0303825 A9	12/2010	Sirbasku	2012/0128683 A1	5/2012	Shantha
2010/0312137 A1	12/2010	Gilmour et al.	2012/0128733 A1	5/2012	Perrin et al.
2010/0316724 A1	12/2010	Whitfield et al.	2012/0128777 A1	5/2012	Keck et al.
2010/0322884 A1	12/2010	Dipietro et al.	2012/0129773 A1	5/2012	Geier et al.
2010/0330168 A1	12/2010	Gicquel et al.	2012/0129819 A1	5/2012	Vancaillie et al.
2011/0028439 A1	2/2011	Witt-Enderby et al.	2012/0136013 A1	5/2012	Li et al.
2011/0039814 A1	2/2011	Huatan et al.	2012/0142645 A1	6/2012	Marx
2011/0053845 A1	3/2011	Levine et al.	2012/0148670 A1	6/2012	Kim et al.
2011/0066473 A1	3/2011	Bernick et al.	2012/0149748 A1	6/2012	Shanler et al.
2011/0076775 A1	3/2011	Stewart et al.	2012/0172343 A1	7/2012	Lindenthal et al.
2011/0076776 A1	3/2011	Stewart et al.	2012/0184515 A1	7/2012	Klar et al.
2011/0086825 A1	4/2011	Chatroux	2012/0231052 A1	9/2012	Sitruk-Ware et al.
2011/0087192 A1	4/2011	Uhland et al.	2012/0232011 A1	9/2012	Kneissel et al.
2011/0091555 A1	4/2011	De Luigi Bruschi et al.	2012/0232042 A1	9/2012	Klar et al.
2011/0098258 A1	4/2011	Masini-Eteve et al.	2012/0263679 A1	10/2012	Marlow et al.
2011/0098631 A1	4/2011	McIntyre et al.	2012/0269721 A1	10/2012	Weng et al.
2011/0104268 A1	5/2011	Pachot et al.	2012/0269878 A2	10/2012	Cantor et al.
2011/0104289 A1	5/2011	Savoir Vilboeuf et al.	2012/0277249 A1	11/2012	Andersson et al.
2011/0130372 A1	6/2011	Agostinacchio et al.	2012/0277727 A1	11/2012	Doshi et al.
2011/0135719 A1	6/2011	Besins et al.	2012/0283671 A1	11/2012	Shibata et al.
2011/0142945 A1	6/2011	Chen et al.	2012/0295911 A1	11/2012	Mannion et al.
2011/0152840 A1	6/2011	Lee et al.	2012/0301517 A1	11/2012	Zhang et al.
2011/0158920 A1	6/2011	Morley et al.	2012/0301538 A1	11/2012	Gordon-Beresford et al.
2011/0171140 A1	7/2011	Illum et al.	2012/0302535 A1	11/2012	Caufriez et al.
2011/0182997 A1	7/2011	Lewis et al.	2012/0316130 A1	12/2012	Hendrix
2011/0190201 A1	8/2011	Hyde et al.	2012/0316496 A1	12/2012	Hoffmann et al.
2011/0195031 A1	8/2011	Du	2012/0321579 A1	12/2012	Edelson et al.
2011/0195114 A1	8/2011	Carrara et al.	2012/0322779 A9	12/2012	Voskuhl
2011/0195944 A1	8/2011	Mura et al.	2012/0328549 A1	12/2012	Edelson et al.
2011/0217341 A1	9/2011	Sah	2012/0329738 A1	12/2012	Liu
2011/0238003 A1	9/2011	Bruno-Raimondi et al.	2013/0004619 A1	1/2013	Chow et al.
2011/0244043 A1	10/2011	Xu et al.	2013/0011342 A1	1/2013	Tamarkin et al.
2011/0250256 A1	10/2011	Hyun-Oh et al.	2013/0017239 A1	1/2013	Viladot Petit et al.
2011/0250259 A1	10/2011	Buckman	2013/0022674 A1	1/2013	Dudley et al.
2011/0250274 A1	10/2011	Shaked et al.	2013/0023505 A1	1/2013	Garfield et al.
2011/0256092 A1	10/2011	Phiasivongsa et al.	2013/0023823 A1	1/2013	Simpson et al.
2011/0262373 A1	10/2011	Umbert Millet	2013/0028850 A1	1/2013	Tamarkin et al.
2011/0262494 A1	10/2011	Achleitner et al.	2013/0029947 A1	1/2013	Nachaegari et al.
2011/0268665 A1	11/2011	Tamarkin et al.	2013/0029957 A1	1/2013	Giliyar et al.
2011/0275584 A1	11/2011	Wilckens et al.	2013/0045266 A1	2/2013	Choi et al.
2011/0281832 A1	11/2011	Li et al.	2013/0045953 A1	2/2013	Sitruk-Ware et al.
2011/0287094 A1	11/2011	Penhasi et al.	2013/0059795 A1	3/2013	Lo et al.
2011/0293720 A1	12/2011	General et al.	2013/0064897 A1	3/2013	Binay
2011/0294738 A1	12/2011	Ren et al.	2013/0072466 A1	3/2013	Choi et al.
2011/0300167 A1	12/2011	McMurry et al.	2013/0084257 A1	4/2013	Ishida et al.
2011/0301087 A1	12/2011	McBride et al.	2013/0085123 A1	4/2013	Li et al.
2011/0306579 A1	12/2011	Stein	2013/0089574 A1	4/2013	Schmidt-Gollwitzer et al.
2011/0311592 A1	12/2011	Birbara	2013/0090318 A1	4/2013	Ulmann et al.
2011/0312927 A1	12/2011	Nachaegari et al.	2013/0102781 A1	4/2013	Bevill et al.
2011/0312928 A1	12/2011	Nachaegari et al.	2013/0108551 A1	5/2013	Langereis et al.
2011/0318405 A1	12/2011	Erwin	2013/0116215 A1	5/2013	Coma et al.
2011/0318431 A1	12/2011	Gulati	2013/0116222 A1	5/2013	Arnold et al.
2012/0009276 A1	1/2012	De Groote	2013/0122051 A1	5/2013	Abidi et al.
2012/0015350 A1	1/2012	Nabatiyan et al.	2013/0123175 A1	5/2013	Hill et al.
2012/0021041 A1	1/2012	Rossi et al.	2013/0123220 A1	5/2013	Queiroz
2012/0028888 A1	2/2012	Janz et al.	2013/0123351 A1	5/2013	Dewitt
2012/0028910 A1	2/2012	Combal et al.	2013/0129818 A1	5/2013	Bernick et al.
2012/0028936 A1	2/2012	Gloger et al.	2013/0131027 A1	5/2013	Pakkalin et al.
2012/0045532 A1	2/2012	Cohen	2013/0131028 A1	5/2013	Snyder et al.
2012/0046264 A1	2/2012	Simes et al.	2013/0131029 A1	5/2013	Bakker et al.
			2013/0149314 A1	6/2013	Bullerdiek et al.
			2013/0164225 A1	6/2013	Tamarkin et al.
			2013/0164346 A1	6/2013	Lee et al.
			2013/0165744 A1	6/2013	Carson et al.



## US 10,052,386 B2

Page 9

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2013/0178452 A1 7/2013 King  
 2013/0183254 A1 7/2013 Zhou et al.  
 2013/0183325 A1 7/2013 Bottoni et al.  
 2013/0189193 A1 7/2013 Tamarkin et al.  
 2013/0189196 A1 7/2013 Tamarkin et al.  
 2013/0189230 A1 7/2013 Shoichet et al.  
 2013/0189368 A1 7/2013 Mosqueira et al.  
 2013/0210709 A1 8/2013 McMurry et al.  
 2013/0216550 A1 8/2013 Penninger et al.  
 2013/0216596 A1 8/2013 Viladot Petit et al.  
 2013/0224177 A1 8/2013 Kim et al.  
 2013/0224257 A1 8/2013 Sah et al.  
 2013/0224268 A1 8/2013 Alam et al.  
 2013/0224300 A1 8/2013 Maggio  
 2013/0225412 A1 8/2013 Sardari Lodriche et al.  
 2013/0225542 A1 8/2013 Poegh et al.  
 2013/0226113 A1 8/2013 Schumacher et al.  
 2013/0243696 A1 9/2013 Wang et al.  
 2013/0245253 A1 9/2013 Marx et al.  
 2013/0245570 A1 9/2013 Jackson  
 2013/0261096 A1 10/2013 Merian et al.  
 2013/0266645 A1 10/2013 Becker et al.  
 2013/0267485 A1 10/2013 Da Silva Maia Filho  
 2013/0273167 A1 10/2013 Lee et al.  
 2013/0274211 A1 10/2013 Burman et al.  
 2013/0280213 A1 10/2013 Voskuhl  
 2013/0316374 A1 11/2013 Penninger et al.  
 2013/0317065 A1 11/2013 Tatani et al.  
 2013/0317315 A1 11/2013 Lu et al.  
 2013/0324565 A1 12/2013 Li et al.  
 2013/0331363 A1 12/2013 Li et al.  
 2013/0338122 A1 12/2013 Bernick et al.  
 2013/0338123 A1 12/2013 Bernick et al.  
 2013/0338124 A1 12/2013 Li et al.  
 2013/0345187 A1 12/2013 Rodriguez Oquendo  
 2014/0018335 A1 1/2014 Tatani et al.  
 2014/0024590 A1 1/2014 Weidhaas et al.  
 2014/0031289 A1 1/2014 Song et al.  
 2014/0031323 A1 1/2014 Perez  
 2014/0066416 A1 3/2014 Leunis et al.  
 2014/0072531 A1 3/2014 Kim et al.  
 2014/0079686 A1 3/2014 Barman et al.  
 2014/0088051 A1 3/2014 Bernick et al.  
 2014/0088058 A1 3/2014 Maurizio  
 2014/0088059 A1 3/2014 Perumal et al.  
 2014/0094426 A1 4/2014 Drummond et al.  
 2014/0094440 A1 4/2014 Bernick et al.  
 2014/0094441 A1 4/2014 Bernick et al.  
 2014/0099362 A1 4/2014 Bernick et al.  
 2014/0100159 A1 4/2014 Conrad  
 2014/0100204 A1 4/2014 Bernick et al.  
 2014/0100205 A1 4/2014 Bernick et al.  
 2014/0100206 A1 4/2014 Bernick et al.  
 2014/0113889 A1 4/2014 Connor et al.  
 2014/0127185 A1 5/2014 Stein et al.  
 2014/0127280 A1 5/2014 Duesterberg et al.  
 2014/0127308 A1 5/2014 Opara et al.  
 2014/0128798 A1 5/2014 Janson et al.  
 2014/0148491 A1 5/2014 Valia et al.  
 2014/0186332 A1 7/2014 Ezrin et al.  
 2014/0187487 A1 7/2014 Shoichet et al.  
 2014/0193523 A1 7/2014 Henry  
 2014/0194396 A1 7/2014 Li et al.  
 2014/0206616 A1 7/2014 Ko et al.  
 2014/0213565 A1 7/2014 Bernick et al.  
 2014/0288035 A1 9/2014 Hubner et al.  
 2014/0329783 A1 11/2014 Bernick et al.  
 2014/0335193 A1 11/2014 Rintoul et al.  
 2014/0370084 A1 12/2014 Bernick et al.  
 2014/0371182 A1 12/2014 Bernick et al.  
 2014/0371183 A1 12/2014 Bernick et al.  
 2014/0371184 A1 12/2014 Bernick et al.  
 2014/0371185 A1 12/2014 Bernick et al.  
 2015/0031654 A1 1/2015 Amadio  
 2015/0045335 A1 2/2015 Bernick et al.

2015/0133421 A1 5/2015 Bernick et al.  
 2015/0196640 A1 7/2015 Cacase et al.  
 2015/0202211 A1 7/2015 Amadio et al.  
 2017/0340739 A1 11/2017 Cacace et al.

## FOREIGN PATENT DOCUMENTS

CA 2856520 A1 5/2013  
 CN 102258455 11/2011  
 CN 102258455 A 11/2011  
 EP 0275716 A1 7/1988  
 EP 0622075 A1 11/1994  
 EP 0785211 A1 1/1996  
 EP 0785212 A1 1/1996  
 EP 0811381 A1 6/1997  
 EP 0785211 A1 7/1997  
 EP 0785212 A1 7/1997  
 EP 0811381 B1 5/2003  
 EP 1094781 B1 7/2006  
 EP 2191833 A1 6/2010  
 EP 2191833 B1 2/2013  
 GB 452238 A 8/1936  
 GB 720561 12/1954  
 GB 720561 A 12/1954  
 GB 848881 A 9/1960  
 GB 874368 8/1961  
 GB 874368 A 8/1961  
 GB 1589946 A 5/1981  
 IN 216026 3/2008  
 IN 2005K000053 9/2009  
 IN 244217 11/2010  
 JP 2007-516259 A 6/2007  
 JP 2009-510127 A 3/2009  
 MX 2014/0006256 A 10/2014  
 WO 1990011064 A1 10/1990  
 WO 1993017686 A1 9/1993  
 WO 1994022426 A1 3/1994  
 WO 1995030409 A1 11/1995  
 WO 1996009826 A2 4/1996  
 WO WO-9619975 A1 7/1996  
 WO 1996030000 A1 10/1996  
 WO 9705491 2/1997  
 WO 1997043989 A1 11/1997  
 WO 1998010293 A1 3/1998  
 WO 1998032465 A1 7/1998  
 WO 1998051280 A1 11/1998  
 WO 1999039700 A1 2/1999  
 WO 1999032072 A1 7/1999  
 WO 1999039700 A1 8/1999  
 WO 1999042109 A1 8/1999  
 WO 9943304 9/1999  
 WO 1999048477 A1 9/1999  
 WO 1999053910 A2 10/1999  
 WO 2000038659 A1 11/1999  
 WO 1999063974 A2 12/1999  
 WO 2000001351 A1 1/2000  
 WO 2000006175 A1 2/2000  
 WO 2000045795 A2 8/2000  
 WO 2000050007 A1 8/2000  
 WO 2000059577 A1 10/2000  
 WO 2001037808 A1 11/2000  
 WO 2000076522 A1 12/2000  
 WO 2002007700 A2 7/2001  
 WO 2001054699 A1 8/2001  
 WO 2001060325 A1 8/2001  
 WO 2002011768 A1 2/2002  
 WO 2002022132 A2 3/2002  
 WO 2002040008 A2 5/2002  
 WO WO-0241878 A2 5/2002  
 WO 2002053131 A1 7/2002  
 WO 2002078602 A3 2/2003  
 WO WO-03028667 A2 4/2003  
 WO 2003041718 A1 5/2003  
 WO 2003041741 A1 5/2003  
 WO 2003068186 A1 8/2003  
 WO 2003077923 A1 9/2003  
 WO 2003082254 A1 10/2003  
 WO 2002078604 A3 11/2003  
 WO 2003092588 A2 11/2003

## US 10,052,386 B2

Page 10

(56)

## References Cited

## FOREIGN PATENT DOCUMENTS

WO	WO-2004014397	A1	2/2004	WO	WO-2013035101	A1	3/2013
WO	WO-2004014432	A1	2/2004	WO	WO-2013044067	A1	3/2013
WO	2004017983	A1	3/2004	WO	WO-2013045404	A2	4/2013
WO	2005027911	A1	3/2004	WO	WO-2013059285	A1	4/2013
WO	2004032897	A2	4/2004	WO	WO 2013/078422	A2	5/2013
WO	2004052336	A2	6/2004	WO	WO-2013063279	A1	5/2013
WO	2005120517	A1	6/2004	WO	WO-2013064620	A1	5/2013
WO	2004054540	A2	7/2004	WO	WO-2013071281	A1	5/2013
WO	2004080413	A2	9/2004	WO	WO-2013088254	A1	6/2013
WO	2005030175	A1	4/2005	WO	WO-2013102665	A1	7/2013
WO	2005087194	A1	9/2005	WO	WO-2013106437	A1	7/2013
WO	2005087199	A2	9/2005	WO	WO-2013113690	A1	8/2013
WO	WO-2005081825	A2	9/2005	WO	WO-2013124415	A1	8/2013
WO	2005105059	A1	11/2005	WO	WO-2013127727	A1	9/2013
WO	2005115335	A1	12/2005	WO	WO-2013127728	A1	9/2013
WO	2005120470	A1	12/2005	WO	WO-2013144356	A1	10/2013
WO	2005120517	A1	12/2005	WO	WO-2013149258	A2	10/2013
WO	2006013369	A2	2/2006	WO	WO-2013158454	A2	10/2013
WO	2006034090	A1	3/2006	WO	WO-2013170052	A1	11/2013
WO	2006036899	A2	4/2006	WO	2013192248	A1	12/2013
WO	2006053172	A2	5/2006	WO	2013192249	A1	12/2013
WO	2006105615	A1	10/2006	WO	2013192250	A1	12/2013
WO	2006113505	A2	10/2006	WO	2013192251	A1	12/2013
WO	2006138686	A1	12/2006	WO	WO-2013178587	A1	12/2013
WO	2006138735	A2	12/2006	WO	WO-2013181449	A1	12/2013
WO	2007045027	A1	4/2007	WO	WO-2014001904	A1	1/2014
WO	WO 2007/038796	A1	4/2007	WO	WO-2014004424	A1	1/2014
WO	2007103294	A2	9/2007	WO	WO-2014009434	A1	1/2014
WO	2006138735	A3	10/2007	WO	WO-2014018569	A1	1/2014
WO	WO-2007120868	A2	10/2007	WO	WO-2014018570	A1	1/2014
WO	2007123790	A1	11/2007	WO	WO-2014018571	A2	1/2014
WO	2007124250	A2	11/2007	WO	WO-2014018856	A1	1/2014
WO	2007124250	A3	12/2007	WO	WO-2014018932	A2	1/2014
WO	2007144151	A1	12/2007	WO	WO-2014031958	A1	2/2014
WO	2007103294	A3	4/2008	WO	WO-2014041120	A1	3/2014
WO	2008049516	A3	5/2008	WO	WO-2014052792	A1	4/2014
WO	2008049516	A3	6/2008	WO	WO-2014056897	A1	4/2014
WO	2008152444	A2	12/2008	WO	WO-2014066442	A2	5/2014
WO	2009002542	A1	12/2008	WO	WO-2014074846	A1	5/2014
WO	2009036311	A1	3/2009	WO	WO-2014076231	A1	5/2014
WO	2009040818	A2	4/2009	WO	WO-2014076569	A2	5/2014
WO	2008152444	A3	6/2009	WO	WO-2014081598	A1	5/2014
WO	2009069006	A2	6/2009	WO	WO-2014086739	A1	6/2014
WO	2009098072	A2	8/2009	WO	WO-2014093114	A1	6/2014
WO	2009098072	A3	10/2009	WO	WO-2014104784	A1	7/2014
WO	2009133352	A2	11/2009				
WO	2009069006	A3	12/2009				
WO	2010033188	A2	3/2010				
WO	2009133352	A3	10/2010				
WO	WO-2010146872	A1	12/2010				
WO	2011000210	A1	1/2011				
WO	2011073995	A2	6/2011				
WO	2011073995	A3	8/2011				
WO	2011120084	A1	10/2011				
WO	2011128336	A1	10/2011				
WO	2010033188	A3	11/2011				
WO	2012009778	A2	1/2012				
WO	2012024361	A1	2/2012				
WO	WO-2012055814	A1	5/2012				
WO	WO-2012055840	A1	5/2012				
WO	WO-2012065740	A1	5/2012				
WO	WO-2012098090	A1	7/2012				
WO	WO-2012116277	A1	8/2012				
WO	WO-2012118563	A2	9/2012				
WO	WO-2012120365	A1	9/2012				
WO	WO-2012127501	A2	9/2012				
WO	WO-2012156561	A1	11/2012				
WO	WO-2012156822	A1	11/2012				
WO	WO-2012158483	A2	11/2012				
WO	WO-2012166909	A1	12/2012				
WO	WO-2012170578	A1	12/2012				
WO	WO-2013011501	A1	1/2013				
WO	2012009778	A3	2/2013				
WO	WO-2013025449	A1	2/2013				
WO	WO-2013028639	A1	2/2013				

## OTHER PUBLICATIONS

Application Note JASCO CD Spectra of Pharmaceuticals Substances Steroids, 2 pages.

Archer, D.F., et al., "Effects of Ospemifene on the Female Reproductive and Urinary Tracts : Translation From Preclinical Models into Clinical Evidence," Menopause, Lippincott-Raven Publishers, United States (2014).

Archer, F., et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study 9(1):21-31, (1992).  
Ashburn, A.D., et al., "Cardiovascular, Hepatic and Renal Lesions in Mice Receiving Cortisone, Estrone and Progesterone," The Yale Journal of Biology and Medicine 35:329-340, Yale Journal of Biology and Medicine, United States (1963).

Bartosova, L. and Bajgar, J., "Transdermal Drug Delivery in Vitro Using Diffusion Cells," Current Medicinal Chemistry 19(27):4671-4677, Bentham Science Publishers, Netherlands (2012).

Benbow, A.L. and Waddell, B.J., "Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus During Rat Pregnancy," Biology of Reproduction 52(6):1327-1333, Society for the Study of Reproduction, United States (1995).

Blake, E.J., et al., "Single and Multidose Pharmacokinetic Study of a Vaginal Micronized Progesterone insert (Endometrin) Compared with Vaginal Gel in Healthy Reproductive-Aged Female Subjects," Fertility and Sterility 94(4):1296-1301, Elsevier for the American Society for Reproductive Medicine, United States (2010).

Brared Christensson, J., et al., "Positive Patch Test Reactions to Oxidized Limonene: Exposure and Relevance," Contact Dermatitis 71(5):264-272, Wiley, England (2014).

Christen, R.D., et al., "Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin," Journal of Clinical Oncology :



## US 10,052,386 B2

Page 11

(56)

## References Cited

## OTHER PUBLICATIONS

Official Journal of the American Society of Clinical Oncology 11(12):2417-2426, American Society of Clinical Oncology, United States (1993).

Christensson, J.B., et al., "Limonene Hydroperoxide Analogues Differ in Allergenic Activity," *Contact Dermatitis* 59(6):344-352, Wiley, England (2008).

Christensson, J.B., et al., "Limonene Hydroperoxide Analogues Show Specific Patch Test Reactions," *Contact Dermatitis* 70(5):291-299, Wiley, England (2014).

Cicinelli, E., et al., "Direct Transport of Progesterone From Vagina to Uterus," *Obstetrics and Gynecology* 95(3):403-406, Lippincott Williams & Wilkins, United States (2000).

Corbett, S.H., et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina : Focus on Vulvodynia," *Southern Medical Journal* 107(7):433-436, Southern Medical Association, United States (2014).

Critchley, H.O., et al., "Estrogen Receptor Beta, but Not Estrogen Receptor Alpha, Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium," *The Journal of Clinical Endocrinology and Metabolism* 86(3):1370-1378, Endocrine Society, United States (2001).

Diramio, J.A., et al., "Poly(Ethylene Glycol) Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," *Masters of Science Thesis*, University of Georgia, Athens, Georgia, 131 pages (2002).

Engelhardt, H., et al., "Conceptus influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy," *Biology of Reproduction* 66(6):1875-1880, Society for the Study of Reproduction, United States (2002).

Ettinger, B., et al., "Comparison of Endometrial Growth Produced by Unopposed Conjugated Estrogens or by Micronized Estradiol in Postmenopausal Women," *American Journal of Obstetrics and Gynecology* 176(1 Pt1):112-117, Elsevier, United States (1997).

Excipients for Pharmaceuticals, Sasol Olefins & Surfactants GMBH, 28 pages (2010).

Filipsson, F., et al., "Concise International Chemical Assessment Document 5," Limonene, first draft, World Health Organization, Geneva, 36 pages (1998).

Final Office Action dated Oct. 26, 2012 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.

Flyvholm, M.A. and Menne, T., "Sensitizing Risk of butylated Hydroxytoluene Based on Exposure and Effect Data," *Contact Dermatitis* 23(5):341-345, Wiley, England (1990).

Franklin, R.D. and Kutteh, W.H., "Characterization of Immunoglobulins and Cytokines in Human Cervical Mucus : influence of Exogenous and Endogenous Hormones," *Journal of Reproductive Immunology* 42(2):93-106, Elsevier/North-Holland Biomedical Press, Ireland (1999).

Franz, T.J., et al., "Use of Excised Human Skin to Assess the Bioequivalence of Topical Products," *Skin Pharmacology and Physiology* 22(5):276-286, Karger, Switzerland (2009).

Fuchs, K.O., et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," *Cutis* 71(6):481-488, Frontline Medical Communications, United States (2003).

Furness, S., et al., "Hormone therapy in Postmenopausal Women and Risk of Endometrial Hyperplasia," *The Cochrane Database of Systematic Reviews* 8:1-204, Wiley, England (2012).

Gafvert, E., et al., "Free Radicals in Antigen formation: Reduction of Contact Allergic Response to Hydroperoxides by Epidermal Treatment with Antioxidants," *The British Journal of Dermatology* 146(4):649-656, Blackwell Scientific Publications, England (2002).

Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 6 pages (2012).

Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 5 pages (2012).

Gattefossé, "Excipients for Safe and Effective Topical Delivery," <http://drug-dev.com/Main/Back-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#> (2012).

Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 8 pages 2012.

Gillet, J.Y., et al., "induction of Amenorrhea During Hormone Replacement therapy : Optimal Micronized Progesterone Dose a Multicenter Study," *Maturitas* 19(2):103-115, Elsevier/North Holland Biomedical Press, Ireland (1994).

Glaser, R.L., et al., "Pilot Study : Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina," *Gynecologic and Obstetric Investigation* 66(2):111-118, Basel, New York, Karger., Switzerland (2008).

Golatski, C., et al., "Comparative Evaluation of Saliva Collection Methods for Proteome Analysis," *International Journal of Clinical Chemistry* 419:42-46, Elsevier., Netherlands (2013).

Graham, J.D. and Clarke, C.L., "Physiological Action of Progesterone in Target Tissues," *Endocrine Reviews* 18(4):502-519, Endocrine Society, United States (1997).

Groothuis, P.G., et al., "Estrogen and the Endometrium : Lessons Learned From Gene Expression Profiling in Rodents and Human," *Human Reproduction Update* 13(4):405-417, Published for the European Society of Human Reproduction and Embryology by Oxford University Press, England (2007).

Hamid, K.A., et al., "The Effects of Common Solubilizing Agents on the intestinal Membrane Barrier Functions and Membrane Toxicity in Rats," *International Journal of Pharmaceutics* 379(1):100-108, Amsterdam, Elsevier/North-Holland Biomedical Press., Netherlands (2009).

Hatton, J., et al., "Safety and Efficacy of a Lipid Emulsion Containing Medium-Chain Triglycerides," *Clinical Pharmacy* 9(5):366-371, American Society of Hospital Pharmacists, United States (1990).

He, F., et al., "Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia induced by Ovariectomy Combined with Estrogen," *Gynecologic and Obstetric Investigation* 76(1):51-56, Karger., Switzerland (2013).

Helmy, A., et al., "Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats," *Clinical Pharmacology & Biopharmaceutics*, S2, 7 pages (2014).

Hostynek, J., et al., "Predicting absorption of fragrance chemicals through human skin," *Journal of the Society of Cosmetic Chemists* 46:221-229, (1995).

Hurn, P.D. and Macrae, I.M., "Estrogen as a Neuroprotectant in Stroke," *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism* 20(4):631-652, Nature Publishing Group, United States (2000).

Hyder, S.M., et al., "Synthetic Estrogen 17Alpha-Ethinyl Estradiol induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17Beta-Estradiol," *The Journal of Pharmacology and Experimental Therapeutics* 290(2):740-747, American Society for Pharmacology and Experimental Therapeutics, United States (1999).

Josh, S.G., et al., "Detection and Synthesis of a Progestagen-Dependent Protein in Human Endometrium," *Journal of Reproduction and Fertility* 59(2):273-285, Portland Press, England (1980).

Kanno J., et al., "The Oecd Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses : Phase 1," *Environmental Health Perspectives* 109(8):785-794, N. C. National Institute of Environmental Health Sciences., United States (2001).

Karlberg, A.T., et al., "Air Oxidation of D-Limonene (the Citrus Solvent) Creates Potent Allergens," *Contact Dermatitis* 26(5):332-340, Wiley, England (1992).

Karlberg, A.T., et al., "Influence of an Anti-Oxidant on the formation of Allergenic Compounds During Auto-Oxidation of D-Limonene," *The Annals of Occupational Hygiene* 38(2):199-207, Oxford University Press, England (1994).

Kaunitz, A.M. "Extended Duration Use of Menopausal Hormone therapy," *Menopause* 21(6):679-681, Lippincott-Raven Publishers, United States (2014).

Kharode, Y., et al., "The Pairing of a Selective Estrogen Receptor Modulator, Bazedoxifene, with Conjugated Estrogens as a New

(56)

**References Cited****OTHER PUBLICATIONS**

Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention,” *Endocrinology* 149(12):6084-6091, Endocrine Society, United States (2008).

Kim, Y.W., et al., “Safety Evaluation and Risk Assessment of D-Limonene,” *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 16(1):17-38, Informa Healthcare, England (2013).

Kola, K., et al., “Enhancing Mechanism of Labrasol on intestinal Membrane Permeability of the Hydrophilic Drug Gentamicin Sulfate,” *European Journal of Pharmaceutics and Biopharmaceutics : Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik E.V* 64(1):82-91, Elsevier Science, Netherlands (2006).

Komm, B.S., et al., “Bazedoxifene Acetate : A Selective Estrogen Receptor Modulator with Improved Selectivity,” *Endocrinology* 146(9):3999-4008, Endocrine Society, United States (2005).

Kumasaka, T., et al., “Effects of Various forms of Progesterin on the Endometrium of the Estrogen-Primed , Ovariectomized Rat,” *Endocrine Journal* 41(2):161-169, Japan Endocrine Society, Japan (1994).

Kuon, R.J. and Garfield, R.E., “Actions of Progestins for the inhibition of Cervical Ripening and Uterine Contractions to Prevent Preterm Birth,” *Facts, Views & Vision in Obgyn* 4(2):110-119, Flemish Society of Obstetrics & Gynaecology, Belgium (2012).

Kuon, R.J., et al., “A Novel Optical Method to Assess Cervical Changes During Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor,” *American Journal of Obstetrics and Gynecology* 205(1):82.e15-82.e20, Elsevier, United States (2011).

Kuon, R.J., et al., “Pharmacologic Actions of Progestins to inhibit Cervical Ripening and Prevent Delivery Depend on their Properties , the Route of Administration , and the Vehicle,” *American Journal of Obstetrics and Gynecology* 202(5):455.e1-455.e9, Elsevier, United States (2010).

Lanigan, R.S. and Yamarik, T.A., “Final Report on the Safety Assessment of Bht (1),” *International Journal of Toxicology* 21(2):19-94, Sage Publications, United States (2002).

Lapez-Belmonte, J., et al., “Comparative Uterine Effects on Ovariectomized Rats After Repeated Treatment with Different Vaginal Estrogen formulations,” *Maturitas* 72(4):353-358, Elsevier/North Holland Biomedical Press, Ireland (2012).

Lauer, A.C., et al., “Evaluation of the Hairless Rat as a Model for in Vivo Percutaneous Absorption,” *Journal of Pharmaceutical Sciences* 86(1):13-18, Wiley-Liss, United States (1997).

Leonetti, H.B., et al., “Transdermal Progesterone Cream as an Alternative Progestin in Hormone therapy,” *Alternative Therapies in Health and Medicine* 11(6):36-38, InnoVision Communications, United States (2005).

Madishetti, S.K., et al., “Development of Domperidone Bilayered Matrix Type Transdermal Patches : Physicochemical , in Vitro and Ex Vivo Characterization,” *Journal of Faculty of Pharmacy* 18(3):221-229, BioMed Central, England (2010).

Miles, R.A., et al., “Pharmacokinetics and Endometrial Tissue Levels of Progesterone After Administration by intramuscular and Vaginal Routes : A Comparative Study,” *Fertility and Sterility* 62(3):485-490, Elsevier for the American Society for Reproductive Medicine, United States (1994).

Miller, J.A., et al., “Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast,” *Journal of Cancer Therapy* 3(5A), Scientific Research Publishing, United States (2012).

Nilsson, U., et al., “Analysis of Contact Allergenic Compounds in Oxidized d-Limonene,” *Chromatographia* 42:199-205, (1996).

Non Final Office Action dated Dec. 12, 2011 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.

Notice of Allowance dated Sep. 11, 2013 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.

Opinion on Diethylene glycol monoethyl ether, Scientific Committee on Consumer Products, The SCCP adopted this opinion at its 10th plenary, 27 pages (2006).

Outterson, K. “The Drug Quality and Security Act—Mind the Gaps,” *The New England Journal of Medicine* 370(2):97-99, Massachusetts Medical Society, United States (2014).

Palamakula, A., et al., “Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components” *Pharmaceutical Technology* 74-88, (2004).

Panay, N., et al., “The 2013 British Menopause Society & Women’s Health Concern recommendations on hormone replacement therapy,” *Menopause International: The Integrated Journal of Postreproductive Health*, published online May 23, 2013, Sage Publications. <http://min.sagepub.com/content/early/2013/05/23/1754045313489645.1>.

Parasuraman, S., et al., “Blood Sample Collection in Small Laboratory Animals,” *Journal of Pharmacology Pharmacotherapeutics* 1(2):87-93, Medknow Publications and Media, India (2010).

Pfau, J.G., et al., “Selective Facilitation of Sexual Solicitation in the Female Rat by a Melanocortin Receptor Agonist,” *Proceedings of The National Academy of Sciences of The United States of America* 101(27):10201-10204, National Academy of Sciences, United States (2004).

Pickles, V.R. “Cutaneous Reactions to injection of Progesterone Solutions into the Skin,” *British Medical Journal* 2(4780):373-374, British Medical Association, England (1952).

Pinkerton, J.V. “What are the Concerns About Custom-Compounded “Bioidentical” Hormone therapy?,” *Menopause* 21(12):1298-1300, Lippincott-Raven Publishers, United States (2014).

Prausnitz, M.R. and Langer, R., “Transdermal Drug Delivery,” *Nature Biotechnology* 26(11):1261-1268, Nature America Publishing, United States (2008).

Product Safety Assessment, Diethylene Glycol Monoethyl Ether, The Dow Chemical Company Page, 5 Pages (2007).

Provider Data Sheet, “About Dried Blood Spot Testing,” ZRT Laboratory, 3 pages (2014).

Rahn, D.D., et al., “Vaginal Estrogen for Genitourinary Syndrome of Menopause: A Systematic Review,” *Obstetrics and Gynecology* 124(6):1147-1156, Lippincott Williams & Wilkins, United States (2014).

Reisman, S.A., et al., “Topical Application of the Synthetic Triterpenoid Rta 408 Protects Mice From Radiation-induced Dermatitis,” *Radiation Research* 181(5):512-520, Radiation Research Society, United States (2014).

Ross, D., et al., “Randomized , Double-Blind , Dose-Ranging Study of the Endometrial Effects of a Vaginal Progesterone Gel in Estrogen-Treated Postmenopausal Women,” *American Journal of Obstetrics and Gynecology* 177(4):937-941, Elsevier, United States (1997).

Ruan, X. and Mueck, A.O., “Systemic Progesterone therapy—Oral, Vaginal , injections and Even Transdermal ?,” *Maturitas* 79(3):248-255, Elsevier/North Holland Biomedical Press, Ireland (2014).

Salem, H.F. “Sustained-Release Progesterone Nanosuspension Following intramuscular injection in Ovariectomized Rats,” *International Journal of Nanomedicine* 10:943-954, DOVE Medical Press, New Zealand (2010).

Santen, R.J. “Vaginal Administration of Estradiol : Effects of Dose , Preparation and Timing on Plasma Estradiol Levels,” *The Journal of The International Menopause Society* :1-14, Informa Healthcare, England (2014).

Schutte, S.C. and Taylor, R.N., “A Tissue-Engineered Human Endometrial Stroma That Responds to Cues for Secretory Differentiation , Decidualization , and Menstruation,” *Fertility and Sterility* 97(4):997-1003, Elsevier for the American Society for Reproductive Medicine, United States (2012).

Schweikart, K.M., et al., “Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats,” *Toxicologic Pathology* 42(8):1188-1196, Sage Publications, United States (2014).

Shao, R., et al., “Direct Effects of Metformin in the Endometrium: A Hypothetical Mechanism for the Treatment of Women with Pcos

## US 10,052,386 B2

Page 13

(56)

## References Cited

## OTHER PUBLICATIONS

- and Endometrial Carcinoma,” *Journal of Experimental & Clinical Cancer Research* 33:41, BioMed Central, England (2014).
- Shrier, L.A., et al., “Mucosal Immunity of the Adolescent Female Genital Tract,” *The Journal of Adolescent Health* 32(3):183-186, Elsevier, United States (2003).
- Siew, A., et al., “Bioavailability Enhancement with Lipid-Based Durg-Delivery Systems” *Pharmaceutical Technology* 28,30-31, (2014).
- Simon, J.A. “What If the Women’s Health initiative Had Used Transdermal Estradiol and Oral Progesterone instead?,” *Menopause* 21(7):769-783, Lippincott-Raven Publishers, United States (2014).
- Smyth, H.F., et al., “A 2-Yr Study of Diethylene Glycol Monoethyl Ether in Rats,” *Food and Cosmetics Toxicology* 2:641-642, Pergamon Press, England (1964).
- Stanczyk, F.Z., et al., “Therapeutically Equivalent Pharmacokinetic Profile Across Three Application Sites for Ag200-15 , A Novel Low-Estrogen Dose Contraceptive Patch,” *Contraception* 87(6):744-749, Elsevier, United States (2013).
- Sullivan, D.W.Jr., et al., “A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient,” *Food and Chemical Toxicology* 72:40-50, Elsevier Science Ltd, England (2014).
- Sun, J. “D-Limonene : Safety and Clinical Applications,” *Alternative Medicine Review* 12(3):259-264, Alternative Medicine Review, United States (2007).
- Tang, F.Y., et al., “Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat,” *Biology of Reproduction* 31(2):399-413, Society for the Study of Reproduction, United States (1984).
- Tas, M., et al., “Comparison of Antiproliferative Effects of Metformine and Progesterone on Estrogen-induced Endometrial Hyperplasia in Rats,” *Gynecological Endocrinology* 29(4):311-314, Informa Healthcare, England (2013).
- Thomas, P. “Characteristics of Membrane Progesterone Receptor Alpha (Mpralpha) and Progesterone Membrane Receptor Component 1 (Pgmrcl) and their Roles in Mediating Rapid Progesterone Actions,” *Frontiers in Neuroendocrinology* 29(2):292-312, Academic Press, United States (2008).
- Tuleu, C., et al., “Comparative Bioavailability Study in Dogs of a Self-Emulsifying formulation of Progesterone Presented in a Pellet and Liquid form Compared with an Aqueous Suspension of Progesterone,” *Journal of Pharmaceutical Sciences* 93(6):1495-1502, Wiley-Liss, United States (2004).
- Ueda, T., et al., “Topical and Transdermal Drug Products,” *Pharmaceutical Forum* 35(3):750-764, (2009).
- Voegtline, K.M. and Granger, D.A., “Dispatches From the interface of Salivary Bioscience and Neonatal Research,” *Frontiers in Endocrinology* 5:25, Frontiers Research Foundation, Switzerland (2014).
- Waddell, B.J. and Bruce, N.W., “The Metabolic Clearance of Progesterone in the Pregnant Rat : Absence of a Physiological Role for the Lung,” *Biology of Reproduction* 40(6):1188-1193, Society for the Study of Reproduction, United States (1989).
- Walter, L.M., et al., “The Role of Progesterone in Endometrial Angiogenesis in Pregnant and Ovariectomised Mice,” *Reproduction* 129(6):765-777, Reproduction and Fertility by BioScientifica, England (2005).
- Wren, B.G., et al., “Effect of Sequential Transdermal Progesterone Cream on Endometrium , Bleeding Pattern , and Plasma Progesterone and Salivary Progesterone Levels in Postmenopausal Women,” *The Journal of the International Menopause Society* 3(3):155-160, Informa Healthcare, England (2000).
- Wu, X., et al., “Gene Expression Profiling of the Effects of CastRATION and Estrogen Treatment in the Rat Uterus,” *Biology of Reproduction* 69(4):1308-1317, Society for the Study of Reproduction, United States (2003).
- Zava, D. “Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues” *Script*:4-5.
- Zava, D.T., et al., “Percutaneous absorption of progesterone,” *Maturitas* 77:91-92, Elsevier/North Holland Biomedical Press, Ireland (2014).
- Geelen, M.J.H., et al., “Dietary Medium-Chain Fatty Acids Raise and (n-3) Polyunsaturated Fatty Acids Lower Hepatic Triacylglycerol Synthesis in Rats,” *The Journal of Nutrition* 125:2449-2456, American Institute of Nutrition, United States (1995).
- Herman, A and Herman, A.P., “Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review,” *Journal of Pharmacy and Pharmacology* 67(4):473-485, Royal Pharmaceutical Society, England (2014).
- Manson, J.E., et al., “Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women’s Health Initiative Randomized Trials,” *The Journal of the American Medical Association* 310:1353-1368, American Medical Association, United States (2013).
- Notice of Allowance, dated Dec. 10, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 10 pages.
- Notice of Allowance, dated Dec. 10, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 8 pages.
- Notice of Allowance, dated Dec. 15, 2014, in U.S. Appl. No. 14/099,623, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Notice of Allowance, dated Feb. 11, 2015, in U.S. Appl. No. 14/475,864, Bernick, B.A., filed Sep. 3, 2014, 9 pages.
- Notice of Allowance, dated Feb. 13, 2015, in U.S. Appl. No. 14/475,814, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Notice of Allowance, dated Jan. 22, 2015, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 5 pages.
- Notice of Allowance, dated Jul. 14, 2014, in U.S. Appl. No. 14/099,545, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Notice of Allowance, dated Jul. 15, 2014, in U.S. Appl. No. 14/099,571, Bernick, B.A., filed Dec. 6, 2013, 11 pages.
- Notice of Allowance, dated Nov. 26, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Notice of Allowance, dated Nov. 7, 2014, in U.S. Appl. No. 14/099,582, filed Dec. 6, 2013, 14 pages.
- Office Action, dated Apr. 14, 2015, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 9 pages.
- Office Action, dated Apr. 7, 2015, in U.S. Appl. No. 14/624,051, Bernick B.A., filed Feb. 17, 2015, 10 pages.
- Office Action, dated Dec. 8, 2014, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 9 pages.
- Office Action, dated Feb. 18, 2015, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 8 pages.
- Office Action, dated Jul. 18, 2014, in U.S. Appl. No. 14/099,623, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Office Action, dated Jul. 2, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Office Action, dated Jul. 3, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 16 pages.
- Office Action, dated Jul. 30, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Office Action, dated Jun. 17, 2014, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 14 pages.
- Office Action, dated Mar. 12, 2015, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 24 pages.
- Office Action, dated Mar. 27, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 8 pages.
- Office Action, dated Oct. 2, 2014, in U.S. Appl. No. 14/475,864, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Office Action, dated Oct. 1, 2014, in U.S. Appl. No. 14/475,814, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Portman, D., et al., “One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy,” *Menopause* 22(11): 7 pages, The North American Menopause Society, United States (2015).
- Rao, R. and Rao, S., “Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions,” *Journal of Bioequivalence & Bioavailability* 6(4):139-143, Open Access (2014).
- Restriction Requirement, dated Mar. 28, 2014, in U.S. Appl. No. 14/099,571, Bernick, B.A., filed Dec. 6, 2013, 7 pages.



## US 10,052,386 B2

Page 14

(56)

## References Cited

## OTHER PUBLICATIONS

- Restriction Requirement, dated Apr. 14, 2015, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 7 pages.
- Restriction Requirement, dated Apr. 29, 2014, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Dec. 5, 2014, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 7 pages.
- Restriction Requirement, mailed Dec. 5, 2014, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 9 pages.
- Restriction Requirement, dated Jul. 3, 2014, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 6 pages.
- Restriction Requirement, dated Mar. 16, 2015, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 7 pages.
- Restriction Requirement, dated Mar. 20, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Mar. 26, 2015, in U.S. Appl. No. 14/476,040, Bernick, B.A., filed Sep. 3, 2014, 7 pages.
- Restriction Requirement, dated May 13, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Nov. 4, 2014, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 7 pages.
- Schindler, A.E., et al., "Classification and pharmacology of progestins," *Maturitas* 46S1:S7-S16, Elsevier Ireland Ltd., Ireland (2003).
- Sitruk-Ware, R., "Pharmacological profile of progestins," *Maturitas* 47:277-283, Elsevier Ireland Ltd., Ireland (2004).
- Stanczyk, F.Z., "All progestins are not created equal," *Science* 68:879-890, Elsevier Inc., United States (2003).
- Stanczyk, F.Z., et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," *Menopause* 12(2):232-237, The North American Menopause Society, United States (2005).
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective," *Climacteric* 17(Suppl 2):8-11, International Menopause Society, United Kingdom (2014).
- Stephenson, K., "Transdermal Progesterone: Effects on Menopausal Symptoms and on Thrombotic, Anticoagulant, and Inflammatory Factors in Postmenopausal Women," *International Journal of Pharmaceutical Compounding* 12(4):295-304, IJPC, United States (2008).
- Weintraub, A., "Women Fooled by Untested Hormones From Compounding Pharmacies," *Forbes*, accessed at <http://onforb.es/1LIUm1V>, accessed on Feb. 23, 2015, 3 pages.
- Co-pending U.S. Appl. No. 14/671,655, Inventors Amadio, J., et al., filed Mar. 27, 2015 (Not Yet Published).
- Co-pending U.S. Appl. No. 14/671,651, Inventors Cacase, J., et al., filed Mar. 27, 2015 (Not Yet Published).
- Acarturk, Fusun, *Mucoadhesive Vaginal Drug Delivery Systems, Recent Patents on Drug Delivery & Formulation*, vol. 3, pp. 193-205, 2009, Bentham Science Publishers, Ltd.
- Bhavnani, Bhagu R., et al., *Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy*, *J Clin Endocrin Metab.*, vol. 97(3), Mar. 2012, The Endocrine Society 2011.
- Bhavnani, Bhagu R., et al., *Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ER) and ERa and ERB*, *Endocrinology*, Oct. 2008, vol. 149(10), pp. 4857-4870, The Endocrine Society 2008.
- Du, Joanna Y., et al., *Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood*, *Menopause: The Journal of the North American Menopause Society*, vol. 20(11), pp. 000-000, The North American Menopause Society 2013.
- Fotherby, K., *Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy*, *Contraception*, vol. 54, pp. 59-69, Elsevier Science, Inc. 1996.
- Fuchs, Katie O., et al., *The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study*, *Pharmacology/Cosmetology*, vol. 5(1), 2006.
- Hargrove, Joel T., et al., *Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone*, *Estrogen Replacement Therapy, Obstetrics & Gynecology*, vol. 73(4), pp. 606-612, Apr. 1989, The American College of Obstetricians and Gynecologists.
- ISR and written opinion for PCT/US/13/46442, dated Nov. 1, 2013.
- ISR and written opinion for PCT/US/13/46443, dated Oct. 31, 2013.
- ISR and written opinion for PCT/US/13/46444, dated Oct. 31, 2013.
- ISR and written opinion for PCT/US/13/46445, dated Nov. 1, 2013.
- Kincl, Fred A., et al., *Short Communication, Increasing Oral Bioavailability of Progesterone by Formulation*, *Journal of Steroid Biochemistry*, vol. 9, pp. 83-84 Pergamon Press 1978, Great Britain.
- The Journal of the North American Menopause Society (NAMS), *Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society*, *Menopause*, vol. 20(9), pp. 888-902, The North American Menopause Society 2013.
- Panay, Nick, *The 2013 British Menopause Society & women's Health Concern recommendations on hormone replacement therapy*, *Menopause International, The Integrated Journal of Postreproductive Health*, vol. 0(0), Sage 2013.
- Patel, Dipen, et al., *Transdermal Drug Delivery System: A Review*, *The Pharma Innovation, The Pharma Journal*, vol. 1(4), 2012.
- Sarrel, Philip M., et al., *The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years*, *American Journal of Public Health, Research and Practice*, pp. e1-e6, Published online ahead of print Jul. 18, 2013.
- Shufelt, Chrisandra L., et al., *Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study*, *Menopause: The Journal of The North American Menopause Society (NAMS)*, vol. 21(3), pp. 000-000, The North American Menopause Society 2013.
- Simon, James, et al., *Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet*, *Obstetrics & Gynecology*, vol. 112(5), pp. 1053-1060, pp. 373-402, Nov. 2008.
- Sitruk-Ware, Regine, et al., *Oral Micronized Progesterone, Contraception*, vol. 36(4), Oct. 1987.
- Sitruk-Ware, Regine, *Progesterones in hormonal replacement therapy: new molecules, risks, and benefits*, *Menopause: The Journal of the North American Menopause Society (NAMS)*, vol. 9(1), pp. 6-15, The North American Menopause Society 2002.
- Smith, Nicholas L., et al., *Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens*, *JAMA Intern Med*, pp. e1-e7, published online Sep. 30, 2013.
- Stanczyk, Frank, et al., *Ethinyl estradiol and 17B-estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment*, *Contraception*, vol. 87, pp. 706-727, Elsevier 2013.
- USPTO, Final Office Action dated Jul. 16, 2013 for U.S. Appl. No. 13/684,002.
- USPTO, Non-Final Office Action dated Mar. 20, 2013 for U.S. Appl. No. 13/684,002.
- USPTO, Notice of allowance dated Dec. 6, 2013 for U.S. Appl. No. 13/684,002.
- USPTO, Non-Final Office Action dated Feb. 18, 2014 for U.S. Appl. No. 14/099,545.
- USPTO, Restriction/Election Requirement dated Feb. 20, 2014 for U.S. Appl. No. 14/099,562.
- USPTO, Restriction/Election Requirement dated Mar. 5, 2014 for U.S. Appl. No. 14/099,623.
- Whitehead, M. I., et al., *Absorption and Metabolism of Oral Progesterone*, *The British Medical Journal*, vol. 280(6217), pp. 825-827, Mar. 22, 1980, BMJ Publishing Group, JSTOR.
- Wood, Charles E., et al., *Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys*, *Breast Cancer Res Treat*,

## US 10,052,386 B2

Page 15

(56)

## References Cited

## OTHER PUBLICATIONS

- vol. 101, pp. 125-134, published online Jul. 14, 2006, Springer Science + Business Media B.V. 2006.
- Acog, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician—Gynecologists, ACOG, No. 141, vol. 123, No. 1, Jan. 2014, Obstetrics & Gynecology.
- Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), Scanning vol. 35 pp. 213-221, 2013, Wiley Period., Inc.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.
- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, Steroids, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M., Pressure-tuning infrared and solution Raman spectroscopic studies of 17 $\beta$ -estradiol and several A-ring . . . , Vibrational Spectroscopy 8, Elsevier, pp. 263, 1995.
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, Bollettino Chimico Farmaceutico, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, Acta Pharm. Jugosl., vol. 40 pp. 71-94, 1990.
- Brandstatter-Kuhnert, M., Zur mikroskopischen Identitätsprüfung und zur Polymorphie der Sexualhormone, Acta, vol. 6, pp. 847-853, 1959, Univ. Innsbruck.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Burry, Kenneth A., Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, Am J Obstet Gynecol, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moléculaire de l'Oestradiol Hemihydrate, Acta Cryst., B28 pp. 560, 1972, Bis(dimethyl-o-thiophenylarsine)palladium(II).
- Busetta, Par Bernard, Structure Cristalline et Moléculaire du Complexe Oestradiol-Propanol, Acta Cryst., B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.
- Campsteyn, Par H, et al., Structure Cristalline et Moléculaire de la Progesterone C21H30O2, Acta Cryst., B28 pp. 3032-3042, 1972.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, Revista Mexicana de Física, 50, Suplemento 1 pp. 1-3, 2004.
- Cole, Wayne & Julian, Percy L., Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Commodari, Fernando, Comparison of 17 $\beta$ -estradiol structures from x-ray diffraction and solution NMR, Magn. Reson. Chem., vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progesterone cream in postmenopausal women, The Lancet, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Dideberg, O, et al., Crystal data on progesterone (C21H30O2), desoxycorticosterone (C21H30O3), corticosterone (C21H30O4) and aldosterone . . . , J. Appl. Cryst. vol. 4 pp. 80, 1971.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , Inter. Journal of Pharmaceutics, Elsevier, vol. 363, pp. 40-49, 2009.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, J. Am. Chem. Soc., vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , J. Thermal Anal., vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, SciFinder, Pharmaceutica Acta Helvetiae, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, Pharmaceutical Research, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, Journal of General Internal Medicine, vol. 22, pp. 1030-1034, 2007.
- Giron, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, Thermochemica Acta, vol. 248 pp. 1-59, 1995, Elsevier.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, J. Pharmaceutical & Biomedical Anal., vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, Acta Cryst., vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, Pharm Res, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, Jour. of Mag. Resonance, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, Mol. Pharmacology, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17 $\beta$ -Estradiol Solid Dispersions, Pharmaceutical Development and Tech., vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Idder, Salima, et al., Physicochemical properties of Progesterone, SciFinder, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johnson, William S, et al., Racemic Progesterone, Tetrahedron Letters No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, Drug Dev. & Indus. Pharm., vol. 10(5) pp. 771-787, 1984, Marcel Dekker.

## US 10,052,386 B2

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(56)

## References Cited

## OTHER PUBLICATIONS

- Korkmaz, Filiz, Biophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyszminewski, R. et al., EPR Study of the Stable Radical in a  $\gamma$ -Irradiated Single Crystal of Progesterone, *Jour. of Mag. Resonance*, vol. 46 pp. 300-305, 1982, Academic Press.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Stein, Emily A. et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A. et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A. et al., Progesterone, SciFinder Scholar Search, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Struhar, M. et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M. et al., The light sensitivity of corticosteroids in crystalline form, *Pharmaceutica acta Helvetica*, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S. et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , *Intl. J. of Pharmaceut.*, vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R. et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, *AAPS PharmSciTech*, vol. 11, No. 3, Sep. 2010.
- USP Monographs: Progesterone, USP29, [www.pharmacopeia.cn/v29240/usp29nf24s0\\_m69870.html](http://www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html), search done: Feb. 25, 2014.
- Utian, Wulf H. et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . Fertility and Sterility, vol. 75(6) pp. 1065, Jun. 2001.
- Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, *Thermochimica Acta* 485, Elsevier, pp. 57, 2009.
- Yalkowsky, Samuel H. & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, *J. of Pharmaceutical Sciences*, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, Handbook of Aqueous Solubility Data, Solutions, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
- Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, *Journal of Steroid Biochem & Mol Biology*, vol. 86 pp. 477-486, 2003.
- Kubli-Garfias, C. et al., Ab initio calculations of the electronic structure of glucocorticoids, *Jour. of Mol. Structure, Theochem*, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, *Jour. of Mol. Structure, Theochem* vol. 425, pp. 171-179, 1998, Elsevier.
- Kuhnert-Brandstaetter, M & Kofler, A, Zur Unterscheidung von lösungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II. vol. 1 pp. 127-139, 1968, *Mikrochimica Acta*.
- Kuhnert-Brandstaetter, M & Linder, R, Zur Hydratbildung bei Steroidhormonen, *Sci. Pharm.*, vol. 41(2) pp. 109-116, 1973.
- Kuhnert-Brandstaetter, M, Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , *Drug Development and Industrial Pharmacy*, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W. et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steroids, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B. et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G., et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , *Maturitas, The European Menopaus Journal*, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroidal conformation of 17 $\alpha$ - and 17 $\beta$ -estradiol in the absence and presence of lipids . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17 $\beta$  and Progesterone Concentrations in Uterine Lymph and Systemic Blood . . . , *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, *Catalent Pharma Solutions*, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MONO1500003758.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between  $\alpha$ - and  $\beta$ -Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*, 35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://lxsr7.oru.edu/~alang/onsc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res*, vol. 31(1), pp. 111-116, 2008.



## US 10,052,386 B2

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(56)

## References Cited

## OTHER PUBLICATIONS

- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estradiol-1,3,5(10)-triene-3,17 $\beta$ -diol solvate: estradiol-methanol-water, *Crystal Structure Comm., Int'l Union of Crystallography*, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gisela L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Progynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Progynova%20TS%20100%2012% 20atches\_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-99, 1998, Plenum Pub. Corp.
- Salole, Eugene G., Estradiol, *Analytical Profiles of Drug Substances*, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ Base . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, *SciFinder*, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- SciFinder Scholar Prednisone Chemical Properties, *SciFinder*, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, *SciFinder*, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, *SciFinder*, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), *Crystal Structure Comm.*, vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>.
- Acarturk, "Mucoadhesive Vaginal Drug Delivery System," *Recent Patents on Drug Delivery & Formulation*, 3(3):193-205, 2009.
- Fuchs et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," *Aesthetic Dermatology*, 8(1):14-19, 2006.
- Panay et al., "The 2013 British Menopause Society & Women's Health concern recommendations on hormone replacement therapy," DOI: 0.1177/1754045313489645, [min.sagepub.com](http://min.sagepub.com). Menopause International: The Integrated Journal of Postreproductive Health 0(0):1-10, 2013.
- Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," *Drug Development and Industrial Pharmacy*, 35(5):525-547, 2009. Abstract Only.
- Azure Pharma, Inc., "ELESTRIN™—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages, 2009.
- Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," *J. Kor. Pharm. Sci.*, 35(3):173-177, 2005.
- Committee of Obstetric Practice, Committee Opinion—No. 522, *Obstetrics & Gynecology*, 119(4):879-882, 2012.
- Diramio, "Polyethylene Glycol Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia—Masters of Science Thesis, 131 pages, 2004. [http://athenaum.libs.uga.edu/bitstream/handle/10724/7820/diramio\\_jackie\\_a\\_200412\\_ms.pdf?sequence=1](http://athenaum.libs.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1).
- Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," *International Journal of Pharmaceutics*, 147(2):165-171, 1997. Abstract Only.
- Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," *Critical Reviews in Toxicology*, 30(3):307-345, 2000. Abstract Only.
- Knuth et al., "Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations," *Advanced Drug Delivery Reviews*, 11(1-2):137-167, 1993. Abstract Only.
- Lucy et al., "Gonadotropin-releasing hormone at estrus: luteinizing hormone, estradiol, and progesterone during the periestrual and postinsemination periods in dairy cattle," *Biol Reprod.*, 35(2):300-11, 1986. Abstract Only.
- NuGen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, 3 pages, undated.
- NuGest 900™, <http://www.thehormoneshop.net/nugest900.htm>, 4 pages, undated.
- Panchagnula et al., "Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol as a cosolvent: in-vitro, ex-vivo and in-vivo rat studies," *J Pharm Pharmacol.* 43(9):609-14, 1991. Abstract Only.
- Salole, "The physicochemical properties of oestradiol," *Journal of Pharmaceutical & Biomedical Analysis*, 5(7):635-648, 1987.
- Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," *Pharmaceutical Research*, 21(2):201-230, 2004.
- Tahition Noni, "Body Balance Cream," [http://products.tni.com/dominican\\_republic/sa\\_spanish/nonistore/product/3438/3416/](http://products.tni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/), 1 page, undated.
- Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," *Skin Pharmacol Physiol.*, 19:106-121, 2006. [http://www.nanobiotech.igmp.unicamp.br/download/Trommer\\_skin%20penetration-2006rev.pdf](http://www.nanobiotech.igmp.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf).
- International Search Report and Written Opinion for related International Application No. PCT/US13/023309 dated Apr. 9, 2013.
- International Search report for corresponding International Application No. PCT/US12/66406, dated Jan. 24, 2013.
- Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmulMCM, Safety Data Sheet, 2011, Janesville, WI.
- Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of Thevetia peruviana and Hura crepitans Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopocia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index>[Feb. 3, 2014 1:37:50 PM].

## US 10,052,386 B2

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(56)

## References Cited

## OTHER PUBLICATIONS

ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.

Corn Refiners Assoc, Corn Oil, 5th Edition, Washington, D.C., 2006.

Dauqan, Eqbal M. A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACSIT Press, Singapore.

Ferrari, Roseli AP., et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, Piracicaba, Braz.

Gunstone, Frank D., et al., *Vegetable Oils in Food Technology: Composition, Properties and Uses*, Blackwell Publishing, CRC Press, 2002.

Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.

Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.

Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/ Water, [Springerlink.com](http://Springerlink.com), pp. 1-21, Apr. 2011.

Stocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science*, vol. 47, pp. 36-39, 1981.

USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.

USP, Lauroyl Polyoxylglycerides, Safety Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.

USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.

USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.

USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.

USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.

USP, USP Certificate—Corn Oil, Lot G0L404, Jul. 2013.

Weber, E.J., *Corn Lipids*, *Cereal Chem.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.

Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.

PCCA, Apothogram, PCCA, May 2014, Houston, TX.

International Search Report and Written Opinion of International Application No. PCT/US2015/023041, Korean Intellectual Property Office, Republic of Korea, dated Jun. 30, 2015, 14 pages.

Sarpal, K., et al., "Self-Emulsifying Drug Delivery Systems: A Strategy to Improve Oral Bioavailability," *Current Research & Information on Pharmaceuticals Sciences* 11(3):42-49, Niper, India (Jul.-Sep. 2010).

Abdalla, A., et al., "A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: characterization, dissolution, in vitro digestion and incorporation into solid pellets," *Eur J Pharm Sci* 35(5):457-464, Elsevier, Netherlands (2008).

Falconer, J.R., et al., "The Effects of Supercritical Carbon Dioxide Processing on Progesterone Dispersion Systems: A Multivariate Study," *AAPS Pharm. Sci. Tech.* 13(4): 1255-1265, Springer, USA (2012).

Restriction Requirement, dated Feb. 6, 2013, in U.S. Appl. No. 13/684,002, Bernick, B.A., filed Nov. 21, 2012, 9 pages.

Office Action, dated Oct. 7, 2015, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 12 pages.

Office Action, dated Jul. 15, 2016, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 15 pages.

Office Action, dated Apr. 21, 2017, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 13 pages.

Office Action, dated Jul. 2, 2015, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 9 pages.

Notice of Allowance, dated Feb. 10, 2016, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 10 pages.

Office Action, dated Oct. 26, 2015, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 10 pages.

Office Action, dated Nov. 7, 2017, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 12 pages.

Office Action, dated Mar. 30, 2016, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 13 pages.

Office Action, dated Jun. 19, 2015, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 11 pages.

Office Action, dated Mar. 23, 2017, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 12 pages.

Notice of Allowance, dated Sep. 29, 2015, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 9 pages.

Notice of Allowance, dated Aug. 4, 2015, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 11 pages.

Notice of Allowance, dated Jun. 15, 2015, in U.S. Appl. No. 14/476,040, Bernick, B.A., filed Sep. 3, 2014, 9 pages.

Office Action, dated Jul. 20, 2016, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 12 pages.

Office Action, dated Jun. 16, 2017, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 13 pages.

Office Action, dated Oct. 8, 2015, in U.S. Appl. No. 14/624,051, Bernick B.A., filed Feb. 17, 2015, 7 pages.

Notice of Allowance, dated Feb. 1, 2016, in U.S. Appl. No. 14/624,051, Bernick B.A., filed Feb. 17, 2015, 6 pages.

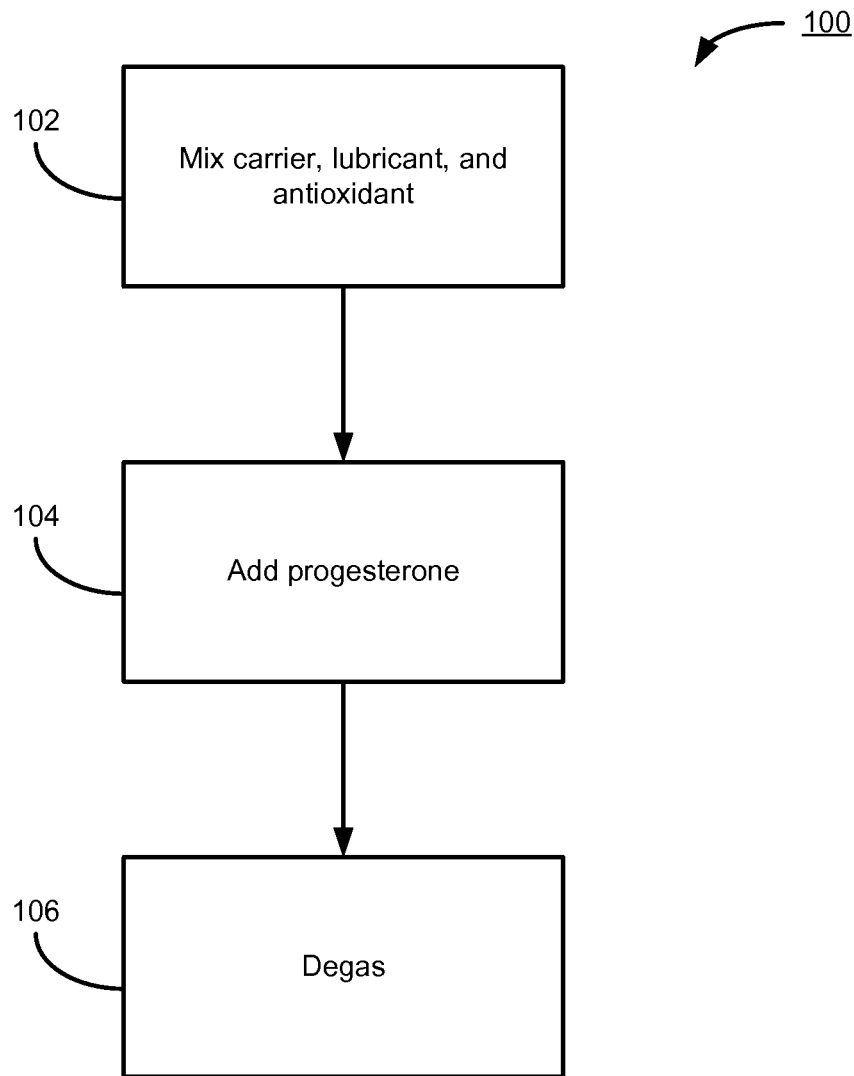
Office Action, dated Sep. 28, 2017, in U.S. Appl. No. 15/454,898, Bernick, B.A., filed Mar. 9, 2017, 10 pages.

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**FIG. 1**

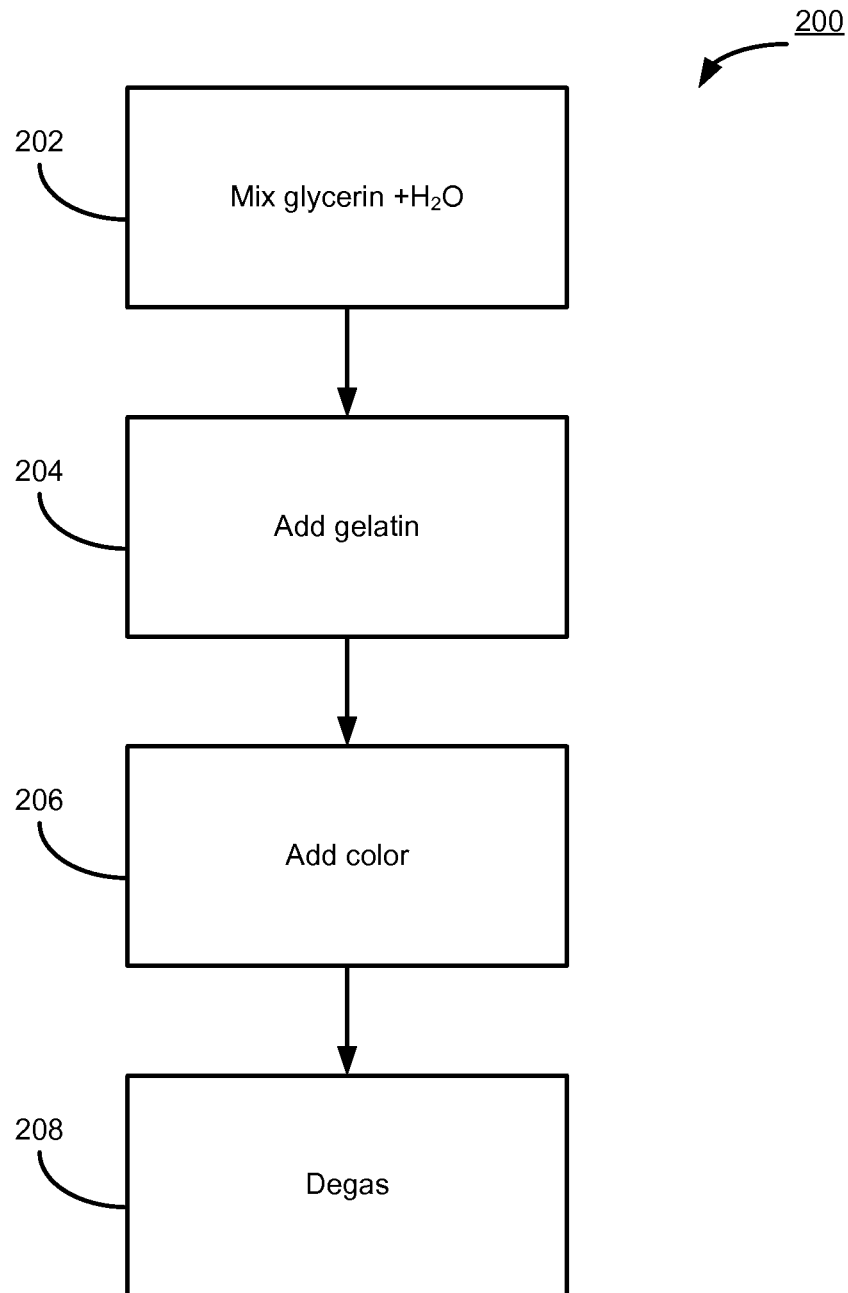
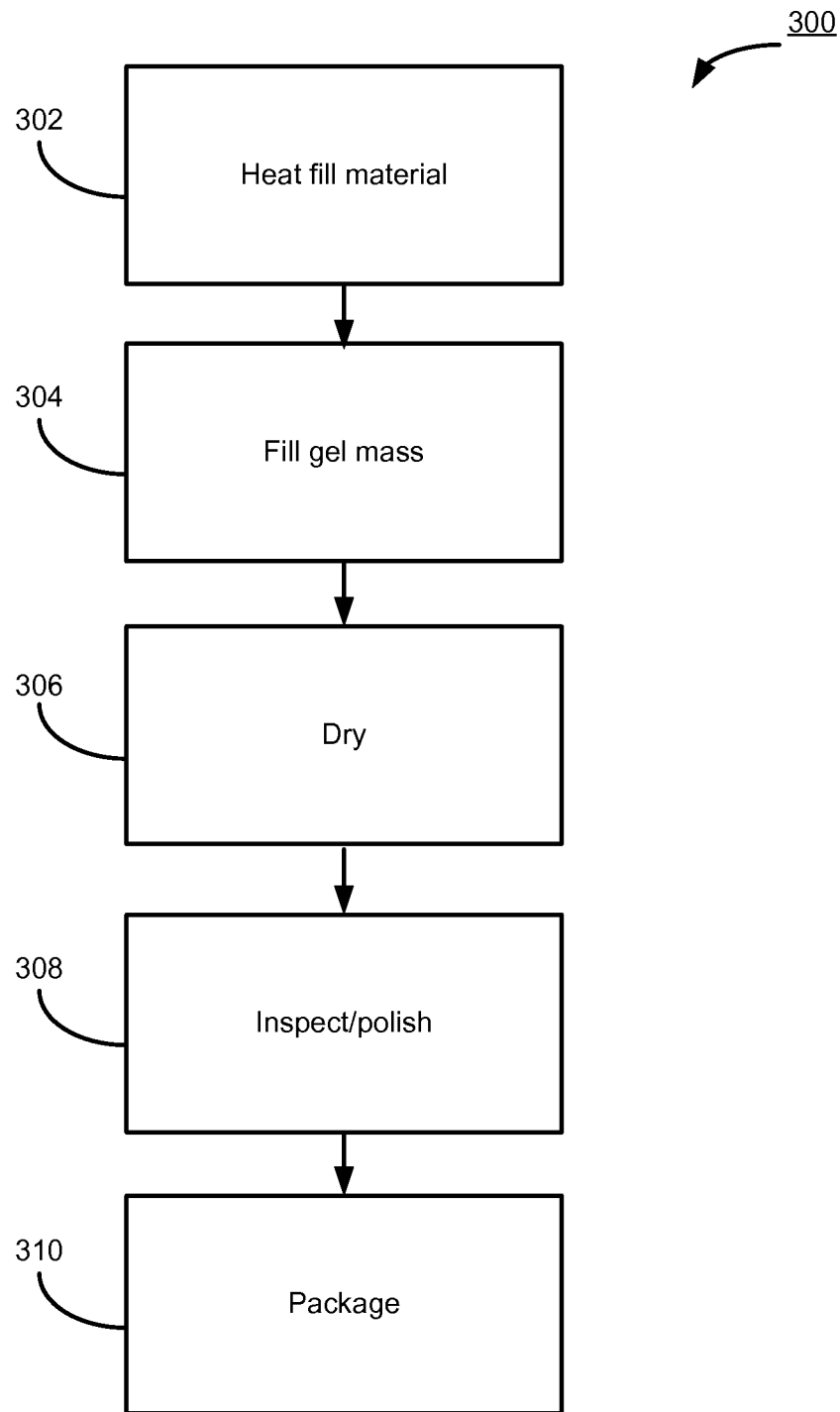
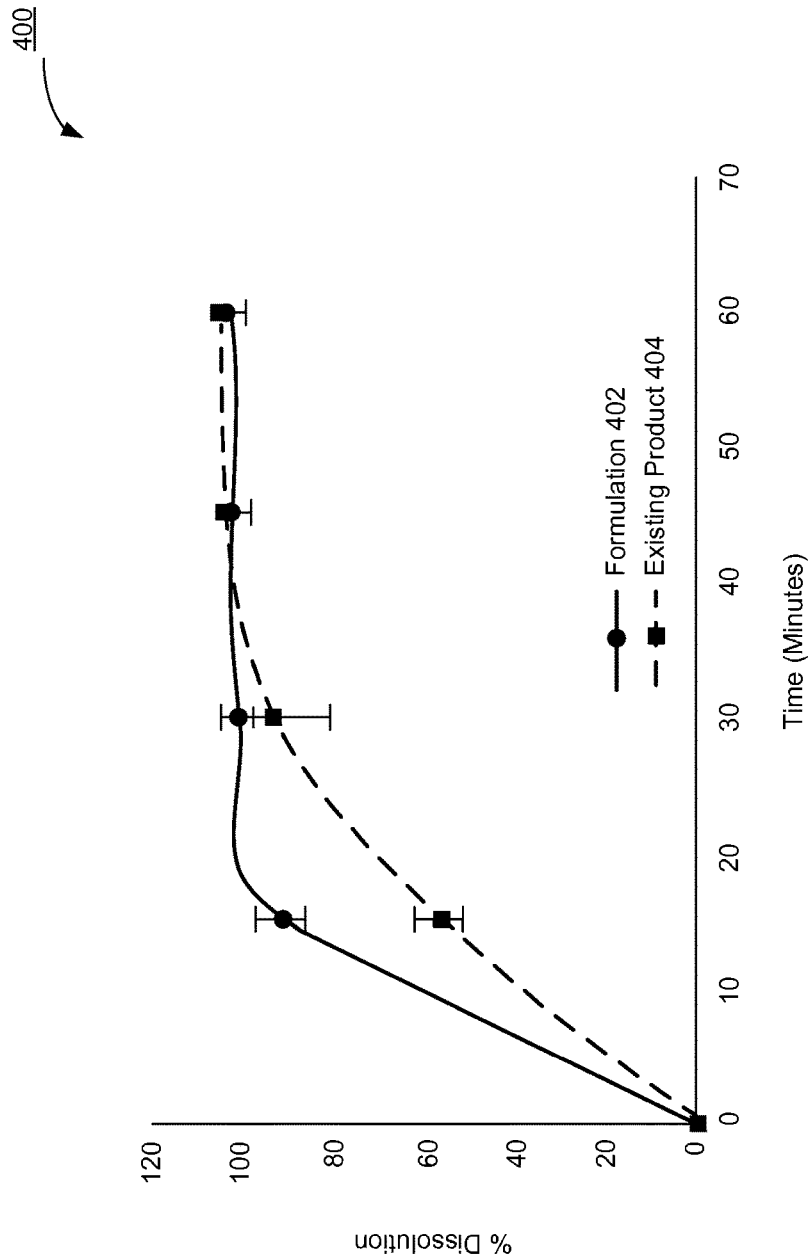


FIG. 2



**FIG. 3**



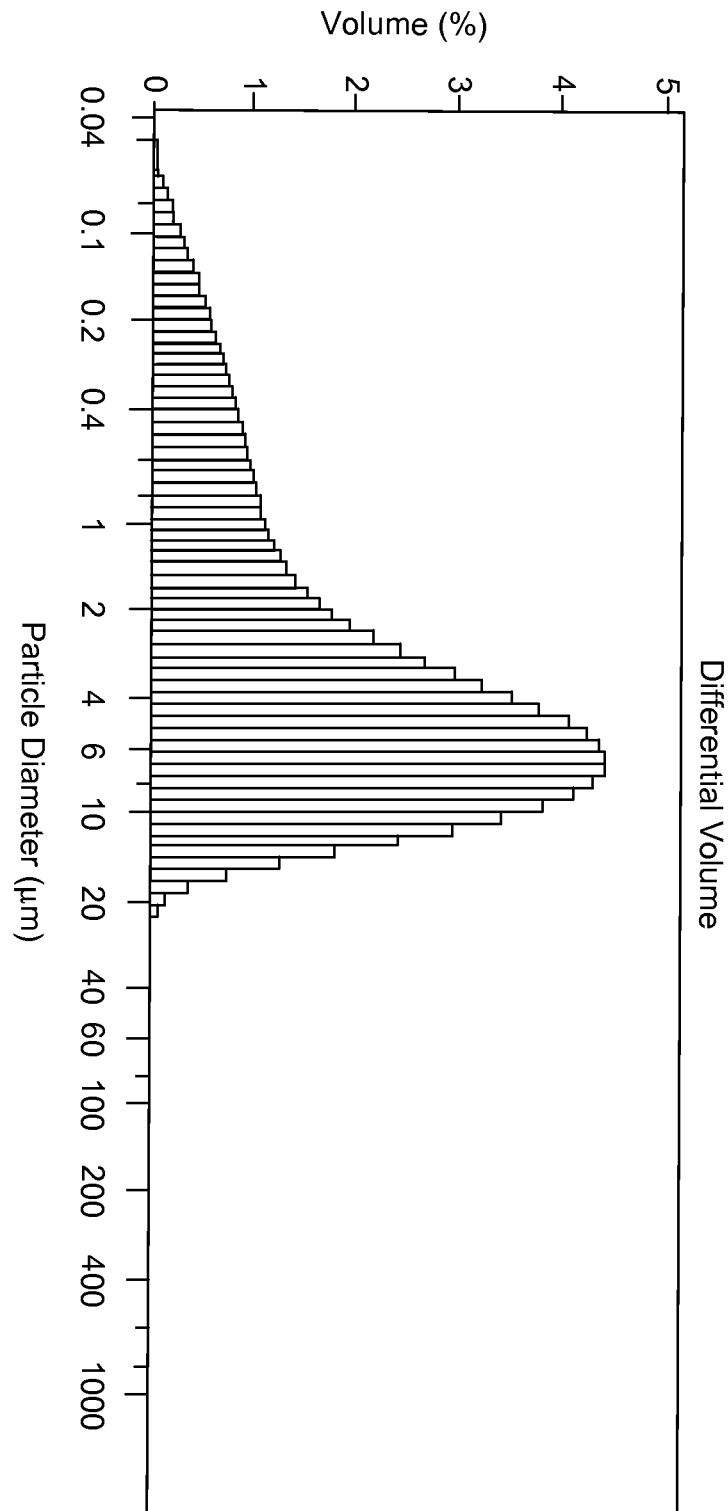


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**FIG. 5**

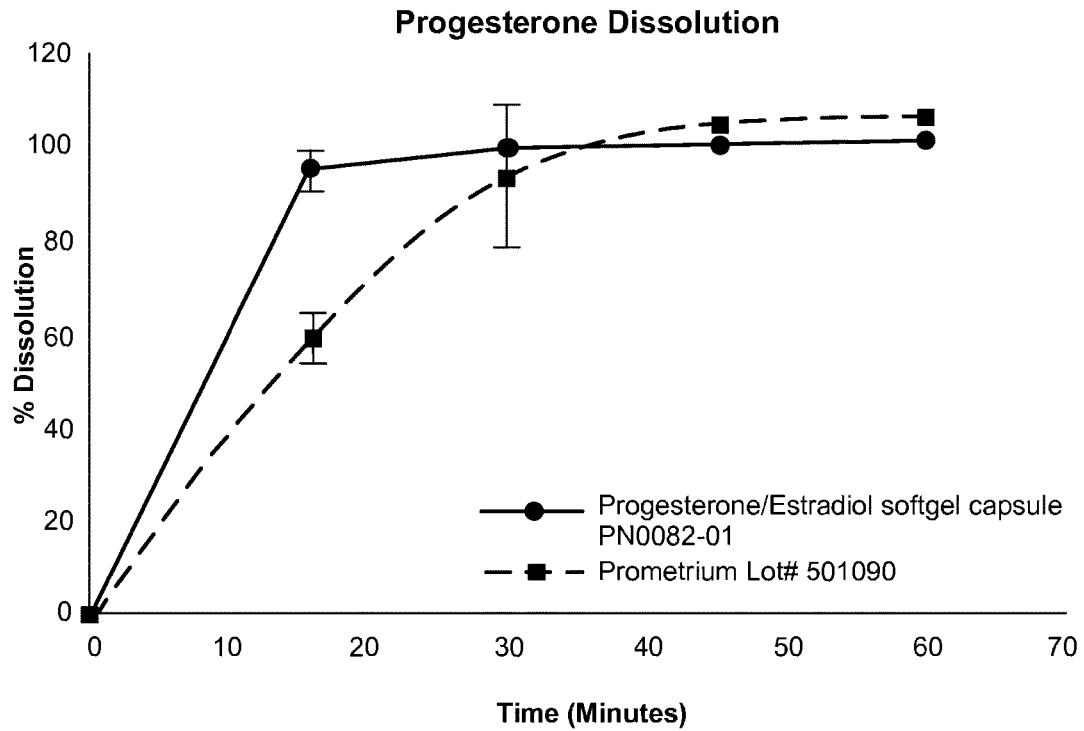


FIG. 6

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**PROGESTERONE FORMULATIONS****CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a National Stage application under 35 U.S.C. § 371 of International Application Ser. No. PCT/US2013/046442, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 18, 2013, and claims priority to the following U.S. Patent Applications: U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS," which was filed on Jun. 20, 2012; U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Nov. 21, 2012; U.S. Patent Application Ser. No. PCT/US2013/023309, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Jan. 25, 2013; U.S. patent application Ser. No. 13/843,362, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Mar. 15, 2013; and U.S. patent application Ser. No. 13/843,428, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Mar. 15, 2013. All aforementioned applications are hereby incorporated by reference herein in their entirety.

**FIELD OF INVENTION**

The disclosure relates to progesterone formulations. Various progesterone formulations may be used in hormone therapies for menopausal, peri-menopausal and post-menopausal females, for example, to mitigate side effects from estrogen replacement therapy. In addition, various progesterone formulations may be used to prevent preterm delivery in pregnant women having a shortened cervix.

**BACKGROUND OF THE INVENTION**

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to supplement hormone levels in women who lack adequate hormone production. It can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones.

HRT is available in various forms. One therapy involves administration of low dosages of one or more estrogen(s) or one or more chemical analogues. Another involves administration of progesterone or one or more chemical analogues. Among other effects, progesterone administration acts to mitigate certain undesirable side effects from estradiol administration or naturally-occurring elevated blood levels including endometrial hyperplasia (thickening) and prevention or inhibition of endometrial cancer. Progesterone is a C-21 steroidal sex hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen. Like other steroids, progesterone consists of four interconnected cyclic hydrocarbons. Progesterone is hydrophobic, having a reported aqueous solubility of  $0.007 \pm 0.0$  mg/ml. Progesterone is poorly absorbed when administered orally.

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Conventional progesterone therapeutics include the administration of PROMETRIUM (progesterone, USP) (Abbott Laboratories, Chicago, Ill.). PROMETRIUM is an FDA-approved drug, formulated in a peanut oil-based medium, containing micronized progesterone, but with a relatively large particle size fraction.

The active ingredient is considered to be structurally identical to naturally occurring progesterone produced by a woman's body (also known as a "bioidentical").

Clinical trials involving PROMETRIUM have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean pharmacokinetic parameters listed in Table 1 (see Table 1, package insert for PROMETRIUM).

TABLE 1

Parameter	Pharmacokinetic Parameters of PROMETRIUM Capsules		
	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
$C_{max}$ (ng/ml)	$17.3 \pm 21.9$	$38.1 \pm 37.8$	$60.6 \pm 72.5$
$T_{max}$ (hr)	$1.5 \pm 0.8$	$2.3 \pm 1.4$	$1.7 \pm 0.6$
AUC (0-10)(ngxh/ml)	$43.3 \pm 30.8$	$101.2 \pm 66.0$	$175.7 \pm 170.3$

The unusually high variability in the  $C_{max}$  and AUC, as evidenced by the large reported standard deviation, indicates that a significant percentage of patients are overdosed or receive a sub-optimal dose.

The presence of peanut oil in the formulation excludes patients who are allergic to peanut oil. Peanut oil, like other peanut products, may act as an allergen. Indeed, there is a portion of the population that has severe reactions to peanut oil. Peanut allergies are becoming a significant health concern. Food allergies are a leading cause of anaphylaxis, with approximately 200 deaths occurring annually in the United States. While incidence and prevalence are not entirely known, it is suspected that about 6% of children and 4% of adults in North America are affected by food allergies. Many food allergies experienced by children are generally outgrown in adulthood with the exception of peanut allergies.

Progesterone and its analogues can be used to treat a variety of medical conditions, including acute diseases or disorders, as well as chronic diseases and disorders associated with long-term declines of natural progesterone levels.

Accordingly, improved formulations of progesterone would be advantageous.

**SUMMARY OF THE INVENTION**

Various pharmaceutical formulations are disclosed herein. For example, pharmaceutical formulations are disclosed comprising ultra-micronized progesterone. Moreover, pharmaceutical formulations are disclosed comprising formulations of ultra-micronized progesterone, wherein the ultra-micronized progesterone is combined with a suitable excipient.

Thus, in various illustrative embodiments, the invention comprises an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical ingredient, in micronized form, in solubilized form, or in micronized and partially soluble form in a carrier that comprises a medium chain fatty

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acid-glycol ester or mixtures thereof and a non-ionic surfactant comprising a polyethylene glycol fatty acid ester. In some such embodiments the progesterone is ultra-micronized. In some such embodiments, at least about 80 wt % of the total progesterone is micronized. The fatty acids can be predominantly (>50 wt %): C6 to C12 fatty acids, C6 to C10 fatty acids, C8 to C12 fatty acids, or C8 to C10 fatty acids, the esters can be mono-, di-, or triesters or mixtures thereof, and the glycols can be glycerol, polyethylene glycol or propylene glycol or mixtures thereof. Some embodiments comprise a non-ionic surfactant that comprises C8 to C18 fatty acid esters of glycerol and polyethylene glycol.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings are included to provide a further understanding of the disclosure and are incorporated in and constitute a part of this specification, illustrate embodiments of the disclosure, and together with the description serve to explain the principles of the disclosure.

FIG. 1 illustrates a process to produce fill material in accordance with various embodiments;

FIG. 2 illustrates a process to produce softgel capsules in accordance with various embodiments;

FIG. 3 illustrates a process to produce softgel capsules in accordance with various embodiments; and

FIG. 4 illustrates a dissolution study of a formulation in accordance with various embodiments.

FIG. 5 illustrates a graph of the particle distribution obtained in Example 10.

FIG. 6 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

#### DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

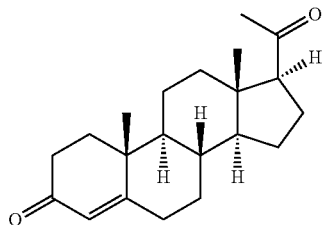
According to various embodiments, a pharmaceutical formulation comprising ultra-micronized progesterone is provided. As described in detail here, various carriers, lubricants, and other excipients may be included. In further embodiments, ultra-micronized progesterone formulations provide improved bioavailability and other pharmacokinetic improvements.

#### Definitions

Unless otherwise specified, the following definitions apply.

The term “ultra-micronized progesterone,” as used herein, includes micronized progesterone having an X50 value below about 20 microns and/or having an X90 value below about 25 microns.

A chemical structure of progesterone is depicted below:



The term “administer,” “administration,” “deliver” or “delivery” (collectively “administration”), as used herein,

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means administration to the body via, without limitation, tablets, capsules, softgel capsules, injections, transdermal patches, creams, gels, vaginal suppositories including gels or other mechanisms known in the art or hereinafter developed. The term “administration” may also mean direct application of softgel contents into the vagina, such as by accessing the softgel contents opening or rupturing the softgel capsule to liberate the contents therein.

The term “X50,” as used herein, means that half of the particles in a sample are smaller in diameter than a given number. For example, ultra-micronized progesterone having an X50 of 5 microns means that, for a given sample of ultra-micronized progesterone, half of the particles have a diameter of less than 5 microns. In that regard, similar terms, in the form XXX mean that XX percent of the particles in the sample are smaller in diameter than a given number. For example, X90 means that ninety percent of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances. For further illustration, C6-C14 fatty acids, C6-C12 fatty acids, and C8-C10 fatty acids are all medium chain fatty acids and may be used in instances in which this specification calls for use of medium chain fatty acids, e.g., medium chain fatty acid esters of glycerol or other glycols.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in gastric juices compared to PROMETRIUM.

The term “gastric juices” means the watery, acidic digestive fluid that is secreted by various glands in the mucous membrane of the stomach and consists chiefly of hydrochloric acid, pepsin, rennin, and mucin.

The term, “API,” as used herein, refers to active pharmaceutical ingredient. In formulations, the API is progesterone.

The term “excipients,” as used herein, refers to non-API substances such as carriers, solvents, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to humans according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “carrier,” as used herein, means any substance or mixture of substances that may be mixed with or contain an API (e.g., ultra-micronized progesterone).

The term “capsule,” as used herein, refers to a generally safe, readily dissolvable enclosure for carrying certain pharmaceutical products, and includes hard or soft shell capsules.

The term “softgel,” includes soft shell capsules, including soft-gelatin capsules and soft vegetable-based capsules, and soft capsules made from other materials providing the composition of such soft capsules are compatible with the formulations of the various embodiments described herein. A softgel may comprise two primary phases: a gel or vegetable-based capsule and a fill material of the pharmaceutical formulation as described herein.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (PK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC,  $C_{max}$  and optionally  $T_{max}$ .

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The terms “pharmacokinetics” and “pharmacokinetic measurements” include assessments and determinations to study absorption, distribution, metabolism, and excretion of a drug.

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone over time.

The term, “ $C_{max}$ ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone over time.

The term, “ $T_{max}$ ” as used herein, refers to the time that it takes for progesterone blood concentration to reach the maximum value.

Optionally, the term, “ $T_{1/2}$ ” as used herein, refers to the time that it takes for progesterone blood concentration to decline to one-half of the maximum level.

Collectively AUC,  $C_{max}$ , and optionally  $T_{max}$  and  $T_{1/2}$ , are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

#### DESCRIPTION

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone, and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %, based on the weight of the entire fill, i.e., the liquid pharmaceutical formulation.

Other embodiments disclosed herein further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, when compared to equal dosages of PROMETRIUM. Blood level variability is also compared at equal sampling times following administration.

According to the PROMETRIUM prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean PK parameters listed in the following table:

Parameter	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
$C_{max}$ (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
$T_{max}$ (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
AUC <sub>0-10</sub> (ngxhr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

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In particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure include the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, “Progesterone-deficient States”) in a subject in need of treatment, and with a non-toxic effective amount of said formulations.

As used herein, the term “treatment”, or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, “prophylaxis” refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the “Beckman Device”) may be used to determine particle size. Particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module (“ULM”). The ULM is capable of suspending samples in the size range of 0.017  $\mu$ m to 2000 nm. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant (“Coulter 1B”), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The



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Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4  $\mu\text{m}$  to 2000  $\mu\text{m}$ . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

In various embodiments, ultra-micronized progesterone has an X50 value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns; and an X90 value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

In various embodiments, ultra-micronized progesterone is formulated with peanut and peanut-oil free excipients.

In various embodiments, the carrier is selected to enhance dissolution and suspension properties of progesterone. In further various embodiments, the carrier is selected to enhance absorption of the API by cells of a mammal. For example, certain carriers may be selected to enhance absorption of the other formulation components, including the API. Absorption may comprise absorption into any cell and particularly absorption into digestive system cells, such as intestinal cells, and cells of the female reproductive system, such as the vagina and the cervix. Selected mono/di/triglycerides are particularly suited to aid in cellular absorption.

In various embodiments, the carrier may comprise medium chain fatty acids. Suitable carriers include caproic fatty acid; caprylic fatty acid; capric fatty acid; lauric acid; myristic acid; linoleic acid; succinic acid; glycerin; propylene glycol; caprylic/capric triglycerides; caproic/caprylic/capric/lauric triglycerides; caprylic/capric/linoleic triglycerides; caprylic/capric/succinic triglycerides; polyethylene glycol; propylene glycol dicaprylate/dicaprate; and combinations and derivatives thereof.

Suitable carriers further include esters of saturated coconut and palm kernel oil and derivatives thereof, including fractionated coconut oils and palm kernel oils thereof; and triglycerides of fractionated vegetable fatty acids, and derivatives thereof and combinations thereof. In further various embodiments, the carrier may comprise one or more monoglycerides, diglycerides, triglycerides, and combinations thereof such a suitable carrier is available commercially under the trademark MIGLYOL (caprylic/capric triglyceride) (Sasol Germany, GmbH). MIGLYOL products comprise esters of saturated coconut and palm kernel oil-derived caprylic and capric fatty acids, glycerin and/or propylene glycol. Suitable MIGLYOL products include MIGLYOL 810 (Caprylic/Capric Triglyceride) MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 818 (Caprylic/Capric/Linoleic Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride).

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Additional examples include a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the CAPMUL brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol:Transcutol); diethylene glycol monoethyl ether; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof. In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL; TRANSCUTOL, MIGLYOL and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM and a non-ionic surfactant; and CAPMUL MCM and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for suspension and/or solubilization of progesterone. CAPMUL MCM and a non-ionic surfactant, e.g., GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, CAPMUL MCM and GELUCIRE were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. Thus, useful ratios can be, e.g., 8:1 or greater, e.g., 60 to 70:1.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In illustrative embodiments, oils used to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, progesterone is soluble in the oils at room temperature, although it may be desirable to warm certain oils initially during manufacture to improve viscosity. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50° C., e.g., at or below 50° C., at or below 40° C., or at or below 50° C. In illustrative embodiments, GELUCIRE 44/14 is heated to about 65° C. and CAPMUL MCM is heated to about 40° C. to facilitate mixing of the oil and non-ionic surfactant, although such heating is not necessary to dissolve the estradiol or progesterone.

In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8



wt % or higher, or 1.0 wt % or higher. Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, CAPMUL MCM, CAPMUL MCM C10 (Glyceryl Monocaprate), CAPMUL MCM C8 (Glyceryl Monocaprylate), and CAPMUL MCM C8 EP (Glyceryl Monocaprylate). These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, MIGLYOL 810 and MIGLYOL 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, CAPMUL PG-8, CAPMUL PG-2L EP/NF (Propylene Glycol Dilaurate), CAPMUL PG-8 NF (Propylene Glycol Monocaprylate), CAPMUL PG-12 EP/NF (Propylene Glycol Monolaurate) and CAPRYOL (Propylene glycol monocaprylate (type II) NF). Other illustrative examples include MIGLYOL 840 (Propylene Glycol Dicaprylate/Dicaprate).

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others, GELUCIRE 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol. Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of GELUCIRE, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids.

It will be understood that commercially available fatty acid esters of glycerol and other glycols are often prepared from natural oils and therefore may comprise components additional to the fatty acid esters that comprise the predominant (by weight) component(s) and that therefore are used to characterize the product. Such other components may be, e.g., other fatty acid triglycerides, mono- and diesters, free glycerol, or free fatty acids. So, for example, when an oil/solubilizing agent is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for CAPMUL MCM C8 describes CAPMUL MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher.

By way of further example, MIGLYOL 812 is generally described as a C8-C10 triglyceride because the fatty acid composition is at least about 80% caprylic (C8) acid and capric (C10) acid. However, it can also comprise small amounts of other fatty acids, e.g., less than about 5% of caproic (C6) acid, lauric (C12) acid, and myristic (C14) acid.

Specifically, a product information sheet for MIGLYOL by SASOL provides the composition of fatty acids as follows:

Tests	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic (C14:0) acid	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

Where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in C8-C10 triglycerides, and a thickening agent, it will be understood that the fatty acid esters component of the formulation may be, e.g., MIGLYOL 812 or a similar product.

By way of further illustration, GELUCIRE 44/14 is generally described as lauroyl polyoxyl-32 glycerides, i.e., polyoxyethylene 32 lauric glycerides (which is a mixture of mono-, di-, and triesters of glycerol and mono- and diesters of PEGs) because the fatty acid composition is 30 to 50% lauric acid and smaller amounts of other fatty acids, e.g., up to 15% caprylic acid, up to 12% capric acid, up to 25% myristic acid, up to 25% palmitic acid, and up to 35% stearic acid. The product may also contain small amounts of non-esterified glycols. Where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising C8 to C18 fatty acid esters of glycerol and polyethylene glycol, it will be understood that the thickening agent component of the formulation may be, e.g., GELUCIRE 44/14 or a similar product.

Similarly, where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising PEG-6 stearate, ethylene glycol palmitostearate, and PEG-32 stearate, it will be understood that the thickening agent component of the formulation may be, e.g., TEFOSE 63 (PEG-6 palmitostearate and ethylene glycol palmitostearate) or a similar product.

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., CAPMUL MCM) and polyethylene glycol glycerides (e.g., GELUCIRE) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65 C in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The progesterone can be added as the mixture cools, e.g., to below about 40 C or to below about 30 C, even down to room temperature.

In certain embodiments, an anionic and/or a non-ionic surfactant is used. Exemplary non-ionic surfactants may include one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as GELUCIRE, including, for example, GELUCIRE 44/11 and GELUCIRE 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, GELUCIRE 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, Tables below. Other non-ionic surfactants include, e.g., LABRASOL (Caprylocaproyl macrogol-8 glycerides EP Caprylocaproyl polyoxyl-8 glycerides NF PEG-8 Caprylic/Capric Glycerides (USA FDA IIG))(Gattefosse) and LABARAFIL (corn/apricot oil PEG-6 esters) (Gattefosse).

In various embodiments, a lubricant is used. Any suitable lubricant may be used, such as, for example and without limitation, lecithin, and in various embodiments, a mixture of polyethylene glycol ("PEG") esters, glycerides, and PEG, such as is commercially available under the trade name GELUCIRE (Gattefosse, FR) may also be used as a lubricant. Suitable lubricants may also comprise calcium stearate,

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ethyl oleate, ethyl laureate, glycerin, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium, oxide, magnesium stearate, poloxamer, glycols, and phospholipid mixtures. In particular, a mixture of polyethylene glycol esters, glycerides, and PEG such as GELUCIRE 44/14, may be used as a lubricant. GELUCIRE 44/14 is a non-ionic water dispersible surfactant, also known as lauroyl macrogol-32 glycerides EP and lauroyl polyoxyl-32 glycerides NF. In various embodiments, GELUCIRE 44/14 acts as a suspension agent.

In various embodiments, an antioxidant is used. Any suitable antioxidant may be used, such as, for example and without limitation, butylated hydroxytoluene. Butylated hydroxytoluene, a derivative of phenol, is lipophilic and is thus suited to being intermixed with ultra-micronized progesterone and carriers disclosed or contemplated herein.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises progesterone, at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of one or more glycols, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized.

Pharmaceutical formulations in accordance with various embodiments comprise ultra-micronized progesterone. In further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, a carrier, and a lubricant. In still further embodiments a pharmaceutical formulation comprises ultra-micronized progesterone, a carrier, a lubricant, and optionally an antioxidant. In still further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, and a medium chain triglyceride as a carrier. In still further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, and monoglycerides/diglycerides/triglycerides of caprylic/capric acid as a carrier. Various further embodiments also comprise lecithin and optionally butylated hydroxytoluene.

In additional embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone and at least one

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carrier, a lubricant, optionally an antioxidant, and other pharmaceutically acceptable excipients. For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

Formulations in accordance with various embodiments may be administered alone or combination with one or more other drugs (or as any combination thereof). For example, formulations in accordance with various embodiments may also comprise estradiol.

In various embodiments, ultra-micronized progesterone is administered in a capsule. Capsules may be prepared using one or more film forming polymers. Suitable film forming polymers include natural polymers, such as gelatin, and synthetic film forming polymers, such as modified celluloses. Suitable modified celluloses include, but are not limited to, hydroxypropyl methyl cellulose, methyl cellulose.

Hard or soft shell capsules can be used to administer the API. In certain embodiments, capsules may be prepared by forming the two capsule halves, filling one of the halves with the fill solution, and then sealing the capsule halves together to form the finished capsule.

Hard shell capsules may be prepared by combining the "Body" and the "Cap". The "Body" of the capsule is filled with the "fill mass" and then closed with the "Cap". The "Body"/"Cap" interface is then sealed/banded.

Soft gelatin capsules may be prepared using a rotary die encapsulation process, as further described below.

Suitable shell additives, for either a hard or soft shell capsules, may include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids, and combinations thereof. The main ingredients of the capsule shell is primarily gelatin (or a gelatin substitute for non-gelatin capsules), plasticizer, and purified water. Hard shell and soft shell capsules differ primarily in the amount of plasticizer present that is used in the capsule shell.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include, but are not limited to, glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light-sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to minimize cross-linking of the gelatin.

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In accordance with various embodiments, a softgel dosage form is used.

A softgel comprises two primary phases: a gel capsule and a fill material. The softgel may comprise a gelatin material in a relatively solid or stiff form. The softgel may define an inner volume that may contain the fill material. Dissolution of the softgel may commence at various points, such as along the digestive tract (mouth, esophagus, stomach and intestines), or other body cavities, such as the vaginal cavity.

As the softgel dissolves, the inner volume may come into fluid communication with the digestive system, allowing the fill material to leach outside the softgel. A softgel may also be punctured, cut, or otherwise opened outside a body. The fill material may then be poured or squeezed outside the gel capsule and applied on or in the body, such as within the vaginal cavity.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl esters (collectively known as "parabens") or combinations thereof.

The fill material may comprise a liquid, such as an oil, a solution, a suspension, or other acceptable forms. The active ingredient or active ingredient may be contained within the liquid.

Formulations in accordance with various embodiments may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Ultra-micronized progesterone in accordance with various embodiments may be formulated as a vaginal suppository or vaginal cream for administration onto the vulva or into the vagina, cervix, or uterus of a human. Capsules (e.g., softgels) containing ultra-micronized progesterone also may be administered vaginally, including insertion of a capsule directly into the vaginal cavity or delivery of such capsule contents into the vaginal cavity. Ultra-micronized progesterone, in accordance with various embodiments, may be formulated for intraperitoneal administration, and atomization, such as with nasal mist administration.

In accordance with various embodiments, enhanced bioavailability of progesterone is provided, such as over conventional progesterone formulations wherein it is well known that commercially available formulations of progesterone are poorly or inconsistently absorbed. While not bound by theory, the elements of the present formulation provide the enhanced performance characteristics as further described herein, including, for example and without limitation, improved bioavailability and the potential to be able to reduce the administered dosage strength compared to presently available progesterone formulations. Bioavailability comparisons to commercially available forms, such as tablet forms, may be determined by standard pharmacokinetic techniques.

In accordance with various embodiments, food effects are reduced, e.g., relative to comparative progesterone products.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

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Capsules may be arranged in blisters or cartridges or bottles.

According to various embodiments, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having delivery days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no API or hormone (e.g., progesterone) may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each dose (e.g., each softgel) may contain ultra-micronized progesterone in amounts of 100 mg, 150 mg, 200 mg, and 250 mg, though other dose ranges are contemplated herein. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Formulations in accordance with various embodiments may be used to treat or prevent preterm delivery in pregnant women, including in certain women having a shortened cervix. In various embodiments, a capsule, for example a softgel capsule, may be opened and the fill material applied in or around the vagina. However, in various embodiments the capsules are taken orally.

Formulations in accordance with various embodiments may be used to treat or prevent endometrial hyperplasia.

Formulations in accordance with various embodiments may be used to treat or prevent secondary amenorrhea.

Formulations in accordance with various embodiments may be used to mitigate or treat the effects of estradiol supplementation. In particular, formulations in accordance with various embodiments may be co-administered with estradiol and/or co-formulated with estradiol.

Formulations in accordance with various embodiments may be used to treat menopause-related symptoms, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy; and osteoporosis and endometrial hyperplasia reduction.

Additional objects of the present disclosure include: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

#### Specific Embodiments

Through extensive trial-and-error testing of various fatty acid esters of glycerol and other glycols, embodiments of the invention have been invented that have one or more favorable characteristics for development as a human drug product. Such favorable characteristics include those described above, e.g., improved PK and reduced variability.

Such embodiments include an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical



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ingredient, in micronized form suspended in a carrier that comprises a medium chain fatty acid-glycol ester or mixtures thereof and a non-ionic surfactant comprising a polyethylene glycol fatty acid ester.

A more specific such embodiment is such formulation wherein the progesterone is ultramicrosized.

In certain such embodiments, the progesterone is suspended and/or solubilized in one or more C6 to C12 fatty acid mono-, di-, or triesters of glycerol, e.g., one or more C6 to C14 triglycerides, e.g., one or more C6 to C12 triglycerides, such as one or more C8-C10 triglycerides. An example of a carrier that provides beneficial properties is C8, C10, or C8 and C10 saturated triglycerides, such as but not limited to MIGLYOL, e.g., MIGLYOL 812.

In such general and more specific embodiments, the non-ionic surfactant is a polyethylene glycol saturated or unsaturated fatty acid ester or diester. In certain such embodiments, the non-ionic surfactant comprises C8 to C18 fatty acid esters of glycerol and polyethylene glycol. An example of a non-ionic surfactant that provides beneficial properties is GELUCIRE, e.g., GELUCIRE 44/14.

In certain such embodiments, the non-ionic surfactant has a HLB value of about 15. An illustrative example of such surfactant is GELUCIRE 44/14.

As noted above, such formulations are liquid at room temperature, not gels, hard fats, or any other solid form. The non-ionic surfactant serves to increase viscosity. In some such embodiments, the non-ionic surfactant, e.g., GELUCIRE or TEFOSE, may be solid at room temperature and require melting to effect mixing with the estradiol solubilized in fatty acid-glycol esters but the resultant formulation is advantageously liquid, not solid.

The formulation of such embodiments is typically encapsulated in a soft gelatin capsule or other soft capsule.

Typically, such formulations do not comprise a bioadhesive (i.e., muco-adhesive) agent, a gelling agent, or a dispersing agent, or, at least, do not comprise one or two of such components.

In more specific such formulations, the capsule shell, the active pharmaceutical ingredient, the fatty acid esters and the non-ionic surfactant are the only essential ingredients. Non-essential ingredients, e.g., colorants, antioxidants or other preservatives, etc., may, of course, be included but other ingredients in amounts that would materially change the solubility of the progesterone, the PK of the encapsulated formulation, or other clinically relevant properties, e.g., other oils or fatty acid esters, lecithin, muco-adherent agents, gelling agents, dispersing agents, or the like would not be included. Such embodiments of the invention may be described as consisting essentially of the capsule shell, the active pharmaceutical ingredient, the fatty acid esters and the non-ionic surfactant, as described in the immediately preceding paragraphs describing illustrative embodiments discovered to have favorable characteristics.

As an example of such embodiments discovered to have such favorable characteristics is mentioned the product identified in Example 2, Table 3, below.

## EXAMPLES

## Example 1

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

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TABLE 2

Ingredient	mg/ Capsule	%	Function
Ultra-micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 2

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 3

Ingredient	%	mg/ Capsule	Function
1. Ultra-micronized Progesterone	30.77	200.00	Active
2. Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
3. Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	3.00	19.50	Suspending Agent
4. Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 3

## Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL, including without limitation MIGLYOL 812, may be used in embodiments comprising a suspension of progesterone.

As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

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Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg.

TABLE 4

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM	73.4
CAPMUL PG8	95
MIGLYOL 812	27.8
CAPMUL MCM: GELUCIRE 44/14 (9:1)	86.4
CAPMUL MCM: GELUCIRE 44/14 (7:3)	70.5
CAPMUL MCM: GELUCIRE 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM in combination with GELUCIRE 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM and GELUCIRE 44/14 system, wherein the ratio of CAPMUL MCM to GELUCIRE 44/14 is 9:1.

TABLE 5

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM:GELUCIRE 44/14 (9:1)	86.4
CAPMUL MCM:GELUCIRE 44/14 (7:3)	70.5
CAPMUL MCM:GELUCIRE 44/14 (6:4)	57.4

## Example 4

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 6

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

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TABLE 7

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 5

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 8

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 6

## Bioavailability Assessment—Fasted

A randomized single-dose oral bioequivalence study comparing 200 mg ultra-micronized progesterone capsule test product (T) and 200 mg PROMETRIUM® (progesterone) capsules (Abbott Laboratories, Abbott Park, Ill.) reference product (R) is conducted. Subjects are administered a single 200 mg dose of either test product (T) or the reference product (R) under fasting conditions, for example, subjects fasted at least 10.0 hours prior to dosing. Blood is collected pre-dose and post-dose. Pre-dose samples are collected at approximately -01.00, -00.50, and 00.00 hours. Post-dose samples are collected at approximately 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 09.00, 10.00, 12.00, 18.00, 24.00, 36.00 and 48.00 hours. Standard meals are provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00 and 37.00 hours post-dose.

Pharmacokinetic measurements are assessed including  $C_{max}$ , AUC and optionally  $T_{max}$ . Comparative bioavailability of the test product (T) and reference product are assessed.

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## Example 7

## Bioavailability Assessment—Fed

The procedures for determining bioavailability under fasted conditions are repeated except that subjects are administered a single 200 mg dose of either test product (T) or reference product (R) immediately following a high fat meal, for example, within 30 minutes of dosing. Blood is collected pre-dose and post-dose. Pre-dose samples are collected at approximately -01.00, -00.50, and 00.00 hours. Post-dose samples are collected at approximately 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 09.00, 10.00, 12.00, 18.00, 24.00, 36.00 and 48.00 hours. Standard meals are provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00 and 37.00 hours post-dose. Pharmacokinetic measurements are assessed including  $C_{max}$ , AUC and optionally  $T_{max}$ . Bioavailability of the test product (T) in reference to the reference product is assessed. The effect of food on the comparative bioavailability of the test product (T) and the reference product (R) are also assessed.

## Example 8

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material, i.e. fill mass, preparation 100 is shown. Step 102 comprises mixing a carrier, a lubricant, and an antioxidant as described herein. For example, lecithin and butylated hydroxytoluene may be mixed with one or more medium chain mono-, di- or triglycerides, or combinations thereof mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $N_2$ . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 104 may comprise mixing ultra-micronized progesterone into the mixture of the carrier, the lubricant, and the antioxidant. A pasty substance is thus formed. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 104 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $N_2$ . Step 106 comprises degassing. The resulting mixture from step 106 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $N_2$ . Heating may be performed until the temperature reaches  $80^{\circ}\pm 5^{\circ}$  C.

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $N_2$ . A vacuum may be drawn in step 204 to de-aerate.

Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $N_2$ . Step 208 comprises degassing. The resulting mixture from step 208 may comprise

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a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to  $30^{\circ}$  C./ $\pm 3^{\circ}$  C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of  $55^{\circ}$  C./ $\pm 10^{\circ}$  C. The wedge temperature may be  $38^{\circ}$  C./ $\pm 3^{\circ}$  C. The drum cooling temperature may be  $4^{\circ}$  C./ $\pm 2^{\circ}$  C. The encapsulator may be lubricated using MIGLYOL 812. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness  $0.85\pm 0.05$  mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight  $\pm 5\%$  (i.e.,  $650\pm 33$  mg and  $325\pm 16.3$  mg).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Polishing may be performed with isopropyl alcohol.

## Example 9

## Stability Study

In accordance with various embodiments, formulations in accordance with various embodiments have an exemplary shelf life of 3 months with storage at  $25\pm 2^{\circ}$  C./ $60\pm 5\%$  RH in 75 cc HDPE white, opaque bottles with a 38/400 mm white child resistant cap.

Packaging during testing comprises a 75 cc round HDPE bottle and 33 mm cap. A Brasken FPT 300F resin is associated with the cap. Testing criteria include visual appearance, assay of progesterone, dissolution, content uniformity and microbial limits testing.

Three test groups are created. Test group 1 comprises a test at  $40^{\circ}$  C./75% RH. Test group 2 comprises a test at  $30^{\circ}$  C./65% RH. Test group 3 comprises a test at  $25^{\circ}$  C./60% RH. Test group 1 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 1, 2, 3, and 6. Test group 2 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 0, 1, 2, 3, 6, and 12. Test group 3 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 0, 1, 2, 3, 6, 12 and 24.

## Example 10

A particle size analysis is conducted by using a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device"). The Beckman Device uses laser diffraction to determine particle size. A sample of a formulation in accordance with various embodiments is provided. The Beckman Device particle sensor yields that the sample has an X50 of 6.67  $\mu$ m, an X75 of 14.78  $\mu$ m, and an X25 of 2.193  $\mu$ m.



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## Example 11

A dissolution study was performed using a formulation in accordance with various embodiments. The results of the dissolution study are shown in FIG. 4.

The dissolution study was performed using a United States Pharmacopoeia dissolution apparatus 3 (reciprocating cylinder) ("USP Apparatus 3"). The USP Apparatus 3 was set to 30 dips per minute. Two hundred fifty mL (250 mL) of a solution of 1N HCL with 3% sodium lauryl sulfate was used at 37° C.

FIG. 4 shows dissolution percentage in the y axis over time in minutes on the x axis. A formulation in accordance with various embodiments is shown having circular dots, and is labeled formulation 402. An existing commercial pharmaceutical product containing progesterone is shown having square dots and is labeled existing product 404. As shown in FIG. 4, formulation 402 reaches a higher level of dissolution in a shorter time than existing product 404.

## Example 12

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 µm, an X75 of 7.442 µm, and an X25 of 1.590 µm. The Beckman Device also yielded that the mean particle size is 4.975 µm, the median particle size is 4.279 µm, the mode particle size is 6.453 µm, and the standard deviation is 3.956 µm. A graph of the particle distribution obtained is shown in FIG. 5.

## Example 13

Study 352—Progesterone and Estradiol Combination Study under Fed Conditions. This following study protocol was used to establish bio-availability and bio-equivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	7.14	50.00
Estradiol Hemihydrate, USP Micronized	0.30	2.07
CAPMUL MCM, NF, USP	83.27	582.93
GELUCIRE 44/14, NF	9.29	650
Total	100.00	700

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The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted to at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of

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heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of  $-70^{\circ}\text{C} \pm 20^{\circ}\text{C}$  in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters  $C_{max}$ ,  $AUC_{0-t}$  &  $AUC_{0-\infty}$  were calculated on data obtained from 24 subjects for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 9, below, for progesterone.

TABLE 9

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean $\pm$ Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
$C_{max}$	47.0	43.0	$81.0 \pm 82.8$	$117.7 \pm 173.7$
$AUC_{0-t}$	107.6	97.8	$163.9 \pm 136.5$	$191.1 \pm 241.7$
$AUC_{0-\infty}$	110.7	110.0	$173.5 \pm 143.0$	$207.1 \pm 250.3$

\*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters  $C_{max}$ ,  $AUC_{0-t}$  &  $AUC_{0-\infty}$  were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 10, below for progesterone.

TABLE 10

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean $\pm$ Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
$C_{max}$	2.3	3.0	$2.9 \pm 2.3$	$3.9 \pm 3.4$
$AUC_{0-t}$	8.4	10.9	$11.2 \pm 8.7$	$14.5 \pm 11.0$
$AUC_{0-\infty}$	12.9	17.2	$15.1 \pm 9.0$	$19.6 \pm 10.2$

\*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to PROMETRIUM.

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## Example 14

## Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of PROMETRIUM and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37 C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from PROMETRIUM. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from PROMETRIUM is attached as FIG. 6.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. The disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad, general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

What is claimed is:

1. A pharmaceutical composition comprising: progesterone;

a medium chain oil; and a non-ionic surfactant;

wherein the progesterone is present from about 20 to about 50 weight percent of the composition.

2. The pharmaceutical composition of claim 1, wherein the progesterone is ultra-micronized and has an X50 less than or equal to 15 microns.

3. The pharmaceutical composition of claim 2, wherein the ultra-micronized progesterone has an X90 of less than about 25 microns.

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4. The pharmaceutical composition of claim 1, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.

5. The pharmaceutical composition of claim 1, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.

6. The pharmaceutical composition of claim 1, wherein the composition is provided in a gelatin capsule.

7. The pharmaceutical composition of claim 1, wherein the composition provides increased bioavailability compared to a micronized progesterone suspended in peanut oil.

8. The pharmaceutical composition of claim 1, wherein progesterone is the sole active ingredient.

9. The pharmaceutical composition of claim 1, wherein the medium chain oil comprises at least one C<sub>6</sub>-C<sub>14</sub> fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.

10. The pharmaceutical composition of claim 9, wherein the at least one C<sub>6</sub>-C<sub>14</sub> fatty acid mono-, di-, or tri-ester of glycerol is a C<sub>8</sub> fatty acid mono-, di-, or tri-ester of glycerol.

11. The pharmaceutical composition of claim 10, further comprising a second C<sub>6</sub>-C<sub>14</sub> fatty acid mono-, di-, or tri-ester of glycerol.

12. The pharmaceutical composition of claim 11, wherein the second C<sub>6</sub>-C<sub>14</sub> fatty acid mono-, di-, or tri-ester of glycerol is a C<sub>10</sub> fatty acid mono-, di-, or tri-ester of glycerol.

13. The pharmaceutical composition of claim 12, wherein the medium chain oil is MIGLYOL 812.

14. A pharmaceutical composition comprising:

75 mg of progesterone;

a medium chain oil; and

a non-ionic surfactant;

wherein the progesterone is present at from about 20 to about 50 weight percent of the composition.

15. The pharmaceutical composition of claim 14, wherein the progesterone is ultra-micronized and has an X50 less than or equal to 15 microns.

16. The pharmaceutical composition of claim 15, wherein the ultra-micronized progesterone has an X90 of less than about 25 microns.

17. The pharmaceutical composition of claim 14, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.

18. The pharmaceutical composition of claim 14, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.

19. The pharmaceutical composition of claim 14, wherein the composition is provided in a gelatin capsule.

20. The pharmaceutical composition of claim 14, wherein the composition provides increased bioavailability compared to a micronized progesterone suspended in peanut oil.

21. The pharmaceutical composition of claim 14, wherein progesterone is the sole active ingredient.

22. The pharmaceutical composition of claim 14, wherein the medium chain oil comprises at least one C<sub>6</sub>-C<sub>14</sub> fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.

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23. The pharmaceutical composition of claim 22, wherein the at least one C<sub>6</sub>-C<sub>14</sub> fatty acid mono-, di-, or tri-ester of glycerol is a C<sub>8</sub> fatty acid mono-, di-, or tri-ester of glycerol.

24. The pharmaceutical composition of claim 23, further comprising a second C<sub>6</sub>-C<sub>14</sub> fatty acid mono-, di-, or tri-ester of glycerol.

25. The pharmaceutical composition of claim 24, wherein the second C<sub>6</sub>-C<sub>14</sub> fatty acid mono-, di-, or tri-ester of glycerol is a C<sub>10</sub> fatty acid mono-, di-, or tri-ester of glycerol.

26. The pharmaceutical composition of claim 25, wherein the medium chain oil is MIGLYOL 812.

27. A pharmaceutical composition comprising:

150 mg progesterone;

a medium chain oil; and

a non-ionic surfactant;

wherein the progesterone is present at from about 20 to about 50 weight percent of the composition.

28. The pharmaceutical composition of claim 27, wherein the progesterone is ultra-micronized and has an X50 less than or equal to 15 microns.

29. The pharmaceutical composition of claim 28, wherein the ultra-micronized progesterone has an X90 of less than about 25 microns.

30. The pharmaceutical composition of claim 27, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.

31. The pharmaceutical composition of claim 27, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.

32. The pharmaceutical composition of claim 27, wherein the composition is provided in a gelatin capsule.

33. The pharmaceutical composition of claim 27, wherein the composition provides increased bioavailability compared to a micronized progesterone suspended in peanut oil.

34. The pharmaceutical composition of claim 27, wherein progesterone is the sole active ingredient.

35. The pharmaceutical composition of claim 27, wherein the medium chain oil comprises at least one C<sub>6</sub>-C<sub>14</sub> fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.

36. The pharmaceutical composition of claim 35, wherein the at least one C<sub>6</sub>-C<sub>14</sub> fatty acid mono-, di-, or tri-ester of glycerol is a C<sub>8</sub> fatty acid mono-, di-, or tri-ester of glycerol.

37. The pharmaceutical composition of claim 36, further comprising a second C<sub>6</sub>-C<sub>14</sub> fatty acid mono-, di-, or tri-ester of glycerol.

38. The pharmaceutical composition of claim 37, wherein the second C<sub>6</sub>-C<sub>14</sub> fatty acid mono-, di-, or tri-ester of glycerol is a C<sub>10</sub> fatty acid mono-, di-, or tri-ester of glycerol.

39. The pharmaceutical composition of claim 38, wherein the medium chain oil is MIGLYOL 812.

40. The pharmaceutical composition of claim 27, wherein the medium chain oil is MIGLYOL 812, the non-ionic surfactant is lauroyl polyoxyl-32-glycerides, and wherein the pharmaceutical formulation provides increased progesterone bioavailability compared to a formulation comprising an equivalent amount of micronized progesterone suspended in peanut oil.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 10,052,386 B2  
APPLICATION NO. : 14/125547  
DATED : August 21, 2018  
INVENTOR(S) : Bernick et al.

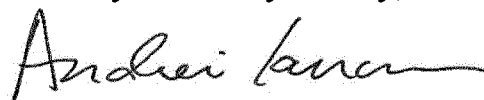
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

In Column 10, Line 31, replace "PEG-6-palmitostearate" with -- PEG-6 stearate --.

Signed and Sealed this  
Twenty-third Day of July, 2019



Andrei Iancu  
*Director of the United States Patent and Trademark Office*

# EXHIBIT L



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(12) **United States Patent**  
**Bernick et al.**

(10) **Patent No.:** **US 10,206,932 B2**

(45) **Date of Patent:** **\*Feb. 19, 2019**

- (54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**
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- (\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 78 days.  
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3,916,899 A	11/1975	Theeuwes et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	6/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes et al.
4,012,496 A	3/1977	Schopflin et al.
4,014,334 A	3/1977	Theeuwes et al.
4,014,987 A	3/1977	Heller et al.
4,016,251 A	8/1977	Higuchi et al.
4,071,623 A	1/1978	van der Vies
4,093,709 A	6/1978	Choi et al.
4,154,820 A	5/1979	Simoons
4,155,991 A	5/1979	Schopflin et al.
4,196,188 A	4/1980	Besins
4,215,691 A	8/1980	Wong
4,237,885 A	12/1980	Wong et al.
4,310,510 A	1/1982	Sherman et al.
4,327,725 A	5/1982	Cortese et al.
4,372,951 A	2/1983	Vorys
4,384,096 A	5/1983	Sonnabend
4,393,871 A	7/1983	Vorhauer et al.
4,402,695 A	9/1983	Wong
4,423,151 A	12/1983	Baranczuk
4,449,980 A	5/1984	Millar et al.
4,610,687 A	9/1986	Fogwell
4,629,449 A	12/1986	Wong
4,732,763 A	3/1988	Beck et al.
4,738,957 A	4/1988	Laurent et al.

(Continued)

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**FOREIGN PATENT DOCUMENTS**

BR	PI1001367-9 A2	7/2012
CA	2612380	12/2006

(Continued)

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- (56) **References Cited**

**U.S. PATENT DOCUMENTS**

1,967,351 A	1/1934	Doisy
2,232,438 A	2/1941	Butenandt
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Beall et al.
3,198,707 A	8/1965	Nomine et al.
3,478,070 A	11/1969	Stein et al.
3,526,648 A	9/1970	Bertin et al.
3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson

**OTHER PUBLICATIONS**

US 6,214,374, 04/2001, Schmirler et al. (withdrawn)  
Pachman et al., "Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions," International Journal of Women's Health, May 7, 2010.\*  
U.S. Appl. No. 13/684,002, filed Nov. 21, 2012, U.S. Pat. No. 8,633,178, Jan. 21, 2014.  
U.S. Appl. No. 13/843,362, filed Mar. 15, 2013.  
U.S. Appl. No. 13/843,428, filed Mar. 15, 2013, U.S. Pat. No. 9,301,920, Apr. 5, 2016.

(Continued)

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(57) **ABSTRACT**

Pharmaceutical compositions for co-administering estradiol and progesterone to a human subject in need thereof are provided. In some embodiments, the pharmaceutical composition comprises solubilized estradiol, suspended progesterone, and a solubilizing agent comprising a medium chain (C6-C12) oil.

**20 Claims, 4 Drawing Sheets**



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(56)

## References Cited

## U.S. PATENT DOCUMENTS

4,756,907 A	7/1988	Beck et al.	5,762,614 A	6/1998	Caillouette
4,762,717 A	8/1988	Crowley, Jr.	5,770,176 A	6/1998	Nargessi
4,788,062 A	11/1988	Gale et al.	5,770,219 A	6/1998	Chiang et al.
4,816,257 A	3/1989	Buster et al.	5,770,220 A	6/1998	Meconi
4,822,616 A	4/1989	Zimmermann et al.	5,770,227 A	6/1998	Dong
4,865,848 A	9/1989	Cheng et al.	5,776,495 A	7/1998	Duclos et al.
4,900,734 A	2/1990	Maxson et al.	5,780,044 A	7/1998	Tipton
4,906,475 A	3/1990	Kim	5,780,050 A	7/1998	Jain
4,942,158 A	7/1990	Sarpotdar et al.	5,788,980 A	8/1998	Nabahi
4,961,931 A	10/1990	Wong	5,788,984 A	8/1998	Schmidt
5,030,629 A	7/1991	Rajadhyaksha	5,789,442 A	8/1998	Garfield et al.
5,064,654 A	11/1991	Berner et al.	5,811,416 A	9/1998	Chwalisz et al.
5,108,995 A	4/1992	Casper	5,811,547 A	9/1998	Nalcamichi et al.
5,128,138 A	7/1992	Blank	5,814,329 A	9/1998	Shah
5,130,137 A	7/1992	Crowley, Jr.	5,820,878 A	10/1998	Shinmura
5,140,021 A	8/1992	Maxson et al.	5,827,200 A	10/1998	Caillouette
5,164,416 A	11/1992	Nagai et al.	5,840,327 A	11/1998	Gale
5,211,952 A	5/1993	Spicer	5,843,468 A	12/1998	Yum
5,252,334 A	10/1993	Chiang et al.	5,843,979 A	12/1998	Wille
5,280,023 A	1/1994	Ehrlich et al.	5,858,394 A	1/1999	Lipp
5,288,496 A	2/1994	Lewis	5,863,552 A	1/1999	Yue
5,340,584 A	8/1994	Spicer et al.	5,866,603 A	2/1999	Li et al.
5,340,585 A	8/1994	Pike et al.	5,869,084 A	2/1999	Paradissis et al.
5,340,586 A	8/1994	Pike et al.	5,882,676 A	3/1999	Yum
5,362,497 A	8/1994	Yamada et al.	5,885,612 A	3/1999	Meconi
5,382,573 A	1/1995	Casper	5,888,533 A	3/1999	Dunn
5,393,528 A	2/1995	Staab	5,891,462 A	4/1999	Carrara
5,393,529 A	2/1995	Hoffmann et al.	5,891,868 A	4/1999	Cummings et al.
5,419,910 A	5/1995	Lewis	5,898,038 A	4/1999	Yallampalli et al.
5,468,736 A	11/1995	Hodgen	5,902,603 A	5/1999	Chen
5,474,783 A	12/1995	Miranda et al.	5,904,931 A	5/1999	Gunther
5,480,776 A	1/1996	Dullien	5,906,830 A	5/1999	Farinas
5,514,673 A	5/1996	Heckenmueller et al.	5,912,010 A	6/1999	Wille
5,516,528 A	5/1996	Hughes et al.	5,916,176 A	6/1999	Caillouette
5,527,534 A	6/1996	Myhling	RE36,247 E	7/1999	Plunkett et al.
5,529,782 A	6/1996	Staab	5,919,477 A	7/1999	Bevan
5,538,736 A	7/1996	Barth	5,922,349 A	7/1999	Elliesen et al.
5,543,150 A	8/1996	Bologna et al.	5,928,666 A	7/1999	Farinas et al.
5,547,948 A	8/1996	Barcomb	5,942,243 A	8/1999	Shah
5,556,635 A	9/1996	Grognet	5,942,531 A	8/1999	Diaz et al.
5,565,199 A	10/1996	Page et al.	5,952,000 A	9/1999	Fikstad
5,567,831 A	10/1996	Li	5,958,446 A	9/1999	Miranda et al.
5,569,652 A	10/1996	Beier et al.	5,962,445 A	10/1999	Stewart
5,580,572 A	12/1996	Liorzou	5,968,919 A	10/1999	Gyurik
5,582,592 A	12/1996	Kendrick	5,972,372 A	10/1999	Saleh et al.
5,585,370 A	12/1996	Casper	5,985,311 A	11/1999	Cordes
5,595,759 A	1/1997	Wright et al.	5,985,850 A	11/1999	Falk
5,595,970 A	1/1997	Garfield et al.	5,985,861 A	11/1999	Levine et al.
5,605,702 A	2/1997	Math	5,993,856 A	11/1999	Ragavan et al.
5,607,691 A	3/1997	Solas	5,989,568 A	12/1999	De Lacharriere
5,607,693 A	3/1997	Bonte	6,001,846 A	12/1999	Edwards et al.
5,609,617 A	3/1997	Cady	6,007,835 A	12/1999	Bon Lapillonne et al.
5,620,705 A	4/1997	Dong et al.	6,010,715 A	1/2000	Pollock
5,626,866 A	5/1997	Heiber	6,013,276 A	1/2000	Teillaud
5,629,021 A	5/1997	Wright	6,022,562 A	2/2000	Autant et al.
5,633,011 A	5/1997	Dong et al.	6,024,974 A	2/2000	Li
5,633,242 A	5/1997	Oettel et al.	6,024,976 A	2/2000	Miranda et al.
5,639,743 A	6/1997	Kaswan et al.	6,028,057 A	2/2000	Burns
5,653,983 A	8/1997	Bonte	6,030,948 A	2/2000	Mann
5,656,286 A	8/1997	Miranda et al.	6,039,968 A	3/2000	Nabahi
5,660,839 A	8/1997	Allec	6,040,340 A	3/2000	Garfield
5,662,927 A	9/1997	Ehrlich	6,056,972 A	5/2000	Hermismeyer
5,663,160 A	9/1997	Dumas	6,060,077 A	5/2000	Meignant
5,676,968 A	10/1997	Lipp et al.	6,068,853 A	5/2000	Berner
5,677,292 A	10/1997	Li et al.	6,074,625 A	6/2000	Hawthorne et al.
5,686,097 A	11/1997	Crisologo	6,077,531 A	6/2000	Salin-Drouin
5,693,335 A	12/1997	Xia	6,080,118 A	6/2000	Blythe
5,694,947 A	12/1997	Lehtinen et al.	6,083,178 A	7/2000	Caillouette
5,700,480 A	12/1997	Hille et al.	6,086,916 A	7/2000	Agnus et al.
5,709,844 A	1/1998	Arbeit et al.	6,087,352 A	7/2000	Trout
5,719,197 A	2/1998	Mantelle	6,090,404 A	7/2000	Meconi et al.
5,735,801 A	4/1998	Caillouette	6,096,338 A	7/2000	Lacy et al.
5,739,176 A	4/1998	Dunn et al.	6,106,848 A	8/2000	Willcox
5,744,463 A	4/1998	Bair	6,117,446 A	9/2000	Place
5,747,058 A	5/1998	Tipton et al.	6,117,450 A	9/2000	Dittgen et al.
			6,124,362 A	9/2000	Bradbury
			6,133,251 A	10/2000	Dittgen et al.
			6,133,320 A	10/2000	Yallampalli et al.
			6,139,868 A	10/2000	Hoffmann

## US 10,206,932 B2

Page 3

(56)

## References Cited

## U.S. PATENT DOCUMENTS

6,139,873	A	10/2000	Hughes, Jr. et al.	6,548,053	B1	4/2003	Murray
6,149,935	A	11/2000	Tenzel	6,548,491	B2	4/2003	Tanabe et al.
6,153,216	A	11/2000	Cordes et al.	6,551,611	B2	4/2003	Elliesen et al.
6,165,491	A	12/2000	Grasset et al.	6,555,131	B1	4/2003	Wolff
6,165,975	A	12/2000	Adams et al.	6,562,367	B1	5/2003	Wolff
6,187,323	B1	2/2001	Aiache et al.	6,562,370	B2	5/2003	Luo
6,187,339	B1	2/2001	de Haan et al.	6,562,790	B2	5/2003	Chein
6,190,331	B1	2/2001	Caillouette	6,569,463	B2	5/2003	Patel et al.
6,201,072	B1	3/2001	Rathi et al.	6,583,129	B1	6/2003	Mazer et al.
6,217,886	B1	4/2001	Rubinstein	6,586,006	B2	7/2003	Roser et al.
6,225,297	B1	5/2001	Stockemann	6,589,549	B2	7/2003	Shih et al.
6,227,202	B1	5/2001	Matapurkar	6,593,317	B1	7/2003	de Ziegler et al.
6,228,383	B1	5/2001	Hansen	6,599,519	B1	7/2003	Seo
6,228,852	B1	5/2001	Shaak	6,610,652	B2	8/2003	Adams et al.
6,242,509	B1	6/2001	MacQueen	6,610,670	B2	8/2003	Blckensfeld et al.
6,245,811	B1	6/2001	Horrobin	6,610,674	B1	8/2003	Schreiber
6,262,115	B1	7/2001	Guittard et al.	6,635,274	B1	10/2003	Carter
6,267,984	B1	7/2001	Hamlin	6,638,528	B1	10/2003	Kanios
6,274,165	B1	8/2001	Meconi	6,638,536	B2	10/2003	Savoir et al.
6,277,418	B1	8/2001	Marakverich et al.	6,645,528	B1	11/2003	Straub et al.
6,283,927	B1	9/2001	Caillouette	6,649,155	B1	11/2003	Dunlop
6,287,588	B1	9/2001	Shih et al.	6,653,298	B2	11/2003	Potter et al.
6,287,693	B1	9/2001	Savoir et al.	6,656,929	B1	12/2003	Agnus et al.
6,294,188	B1	9/2001	Ragavan et al.	6,660,726	B2	12/2003	Hill et al.
6,294,192	B1	9/2001	Patel et al.	6,663,608	B2	12/2003	Rathbone et al.
6,294,550	B1	9/2001	Place et al.	6,663,895	B2	12/2003	Savoir et al.
6,299,900	B1	10/2001	Reed et al.	6,682,757	B1	1/2004	Wright
6,303,132	B1	10/2001	Nelson	6,692,763	B1	2/2004	Cummings et al.
6,303,588	B1	10/2001	Danielov	6,708,822	B1	3/2004	Muni
6,306,841	B1	10/2001	Place et al.	6,720,001	B2	4/2004	Chen
6,306,914	B1	10/2001	de Ziegler et al.	6,737,081	B2	5/2004	Savoir et al.
6,309,669	B1	10/2001	Setterstrom et al.	6,740,333	B2	5/2004	Beckett et al.
6,309,848	B1	10/2001	Howett et al.	6,743,448	B2	6/2004	Kryger
6,312,703	B1	11/2001	Orthofer	6,743,815	B2	6/2004	Huebner et al.
6,328,987	B1	12/2001	Marini	6,747,018	B2	6/2004	Tanabe et al.
6,342,491	B1	1/2002	Dey et al.	6,750,291	B2	6/2004	Kim
6,344,211	B1	2/2002	Hille	6,756,208	B2	6/2004	Griffin et al.
6,372,209	B1	4/2002	Chrisope	6,776,164	B2	8/2004	Bunt et al.
6,372,245	B1	4/2002	Vo	6,787,152	B2	9/2004	Kirby et al.
6,372,246	B1	4/2002	Wei et al.	6,805,877	B2	10/2004	Massara et al.
6,387,390	B1	5/2002	Deaver et al.	6,809,085	B1	10/2004	Elson et al.
6,402,705	B1	6/2002	Caillouette	6,818,226	B2	11/2004	Reed et al.
6,416,778	B1	7/2002	Ragavan et al.	6,821,524	B2	11/2004	Marini
6,420,352	B1	7/2002	Knowles	6,841,716	B1	1/2005	Tsutsumi
6,423,039	B1	7/2002	Rathbone et al.	6,844,334	B2	1/2005	Hill et al.
6,423,683	B1	7/2002	Heaton et al.	6,855,703	B1	2/2005	Hill et al.
6,432,438	B1	8/2002	Shukla	6,860,859	B2	3/2005	Mehrotra et al.
6,436,633	B1	8/2002	Kreider et al.	6,866,865	B2	3/2005	Hsia et al.
6,440,454	B1	8/2002	Santoro et al.	6,869,969	B2	3/2005	Heubner et al.
6,444,224	B1	9/2002	Rathbone et al.	6,878,518	B2	4/2005	Whitehead
6,444,234	B1	9/2002	Kirby et al.	6,901,278	B1	5/2005	Notelovitz
6,451,300	B1	9/2002	Leyba	6,905,705	B2	6/2005	Palm et al.
6,451,339	B2	9/2002	Patel et al.	6,911,211	B2	6/2005	Tamarkin
6,451,779	B1	9/2002	Hesch	6,911,438	B2	6/2005	Wright
6,455,246	B1	9/2002	Howett et al.	6,923,988	B2	8/2005	Patel et al.
6,455,517	B1	9/2002	Tanabe et al.	6,924,274	B2	8/2005	Lardy et al.
6,465,004	B1	10/2002	Houze	6,932,983	B1	8/2005	Straub et al.
6,465,005	B1	10/2002	Biali	6,939,558	B2	9/2005	Massara et al.
6,465,006	B1	10/2002	Zhang	6,943,021	B2	9/2005	Klausner et al.
6,468,526	B2	10/2002	Chrisope	6,958,327	B1	10/2005	Hillisch et al.
6,469,016	B1	10/2002	Place et al.	6,960,337	B2	11/2005	Pike
6,472,434	B1	10/2002	Place et al.	6,962,691	B1	11/2005	Lulla et al.
6,479,232	B1	11/2002	Howett et al.	6,962,908	B2	11/2005	Aloba et al.
6,495,160	B2	12/2002	Esposito	6,967,194	B1	11/2005	Matsuo et al.
6,500,814	B1	12/2002	Hesch	6,974,569	B2	12/2005	Boyd
6,503,896	B1	1/2003	Tanabe et al.	6,977,250	B2	12/2005	Rodriguez
6,511,969	B1	1/2003	Hermesmyer	6,978,945	B2	12/2005	Wong et al.
6,521,250	B2	2/2003	Seibertz	6,995,149	B1	2/2006	Reilhac
6,526,980	B1	3/2003	Tracy et al.	7,004,321	B1	2/2006	Hackbarth
6,528,094	B1	3/2003	Savoir et al.	7,005,429	B2	2/2006	Dey et al.
6,531,149	B1	3/2003	Meconi	7,011,846	B2	3/2006	Shojaei et al.
6,537,580	B1	3/2003	Savoir et al.	7,018,992	B2	3/2006	Koch et al.
6,538,039	B2	3/2003	Laurent	7,030,104	B2	4/2006	Paris
6,544,196	B2	4/2003	Caillouette	7,030,157	B2	4/2006	Ke et al.
6,544,553	B1	4/2003	Hsia et al.	RE39,104	E	5/2006	Duclos et al.
				7,074,779	B2	7/2006	Sui et al.
				7,083,590	B1	8/2006	Bunt et al.
				7,091,213	B2	8/2006	Metcalf, III et al.
				7,094,228	B2	8/2006	Zhang

## US 10,206,932 B2

Page 4

(56)

## References Cited

## U.S. PATENT DOCUMENTS

7,097,853	B1	8/2006	Keister	7,945,459	B2	5/2011	Grace et al.
7,101,342	B1	9/2006	Caillouette	7,960,368	B2	6/2011	Rao
7,105,573	B2	9/2006	Krajcik	7,989,436	B2	8/2011	Hill et al.
7,135,190	B2	11/2006	Piao et al.	7,989,487	B2	8/2011	Welsh et al.
7,153,522	B1	12/2006	Ikeura	8,022,053	B2	9/2011	Mueller et al.
7,163,681	B2	1/2007	Giles-Komar et al.	8,048,017	B2	11/2011	Xu
7,163,699	B2	1/2007	Besse	8,048,869	B2	11/2011	Bunschoten et al.
7,175,850	B2	2/2007	Cevc	8,063,030	B2	11/2011	Ellman
7,179,799	B2	2/2007	Hill et al.	8,071,576	B2	12/2011	Visser
7,196,074	B2	3/2007	Blye et al.	8,071,729	B2	12/2011	Giles-Komar et al.
7,198,800	B1	4/2007	Ko	8,075,916	B2	12/2011	Park
7,198,801	B2	4/2007	Carrara et al.	8,075,917	B2	12/2011	Park
7,226,910	B2	6/2007	Wilson et al.	8,076,317	B2	12/2011	Kulmann
7,247,625	B2	7/2007	Zhang et al.	8,076,319	B2	12/2011	Leonard
7,250,446	B2	7/2007	Sangita et al.	8,080,553	B2	12/2011	Auspitz
7,267,829	B2	9/2007	Kirby et al.	8,088,605	B2	1/2012	Beudet et al.
7,300,926	B2	11/2007	Prokai et al.	8,096,940	B2	1/2012	Iverson
7,303,763	B2	12/2007	Ho	8,101,209	B2	1/2012	Legrand et al.
7,317,037	B2	1/2008	Fensome et al.	8,101,773	B2	1/2012	Smith et al.
7,329,654	B2	2/2008	Kanojia et al.	8,114,152	B2	2/2012	Furst
7,335,650	B2	2/2008	Potter et al.	8,114,434	B2	2/2012	Sasaki et al.
7,374,779	B2	5/2008	Chen et al.	8,114,442	B2	2/2012	Tucker
7,378,404	B2	5/2008	Peters et al.	8,119,741	B2	2/2012	Pavlin
7,381,427	B2	6/2008	Ancira	8,121,886	B2	2/2012	Azar
7,387,789	B2	6/2008	Klose et al.	8,124,118	B2	2/2012	Lennernaes
7,388,006	B2	6/2008	Schmees et al.	8,124,595	B2	2/2012	Boissonneault
7,414,043	B2	8/2008	Kosemund et al.	8,147,561	B2	4/2012	Binmoeller
7,427,413	B2	9/2008	Savoir et al.	8,148,546	B2	4/2012	Baasner
7,427,609	B2	9/2008	Leonard	8,158,613	B2	4/2012	Staniforth
7,429,576	B2	9/2008	Labrie	8,158,614	B2	4/2012	Lambert et al.
7,431,941	B2	10/2008	Besins et al.	8,163,722	B2	4/2012	Savor
7,456,159	B2	11/2008	Houze	8,177,449	B2	5/2012	Watkinson
7,459,445	B2	12/2008	Hill et al.	8,182,833	B2	5/2012	Hermismeyer
7,465,587	B2	12/2008	Imrich	8,187,615	B2	5/2012	Friedman
7,470,433	B2	12/2008	Carrara et al.	8,187,640	B2	5/2012	Dunn
7,485,666	B2	2/2009	Villaneuva et al.	8,195,403	B2	6/2012	Wood, Jr.
7,497,855	B2	3/2009	Ausiello et al.	8,202,736	B2	6/2012	Mousa et al.
7,498,303	B2	3/2009	Arnold	8,217,024	B2	7/2012	Ahmed et al.
7,534,765	B2	5/2009	Gregg et al.	8,221,785	B2	7/2012	Chien
7,534,780	B2	5/2009	Ring	8,222,008	B2	7/2012	Thoene
7,550,142	B2	6/2009	Giles-Komar et al.	8,222,237	B2	7/2012	Narkunan
7,563,565	B1	7/2009	Matsuo et al.	8,227,454	B2	7/2012	Hill et al.
7,569,274	B2	8/2009	Alphonse	8,227,509	B2	7/2012	Castro et al.
7,572,779	B2	8/2009	Aloba et al.	8,241,664	B2	8/2012	Dudley et al.
7,572,780	B2	8/2009	Hermismeyer	8,247,393	B2	8/2012	Ahmed et al.
7,589,082	B2	9/2009	Savoir et al.	8,257,724	B2	9/2012	Cromack
7,671,027	B2	3/2010	Loumaye	8,257,725	B2	9/2012	Cromack
7,674,783	B2	3/2010	Hermismeyer	8,268,352	B2	9/2012	Karan
7,687,281	B2	3/2010	Roth et al.	8,268,806	B2	9/2012	Labrie
7,687,485	B2	3/2010	Levinson et al.	8,268,878	B2	9/2012	Johnson
7,694,683	B2	4/2010	Callister et al.	8,273,730	B2	9/2012	Fernandez et al.
7,704,983	B1	4/2010	Hodgen et al.	8,287,888	B2	10/2012	Song et al.
7,727,720	B2	6/2010	Dhallan	8,288,366	B2	10/2012	Gonzalez
7,732,408	B2	6/2010	Josephson et al.	8,318,898	B2	11/2012	Fasel
7,749,989	B2	7/2010	Hill et al.	8,324,193	B2	12/2012	Sepsick
7,767,656	B2	8/2010	Shoichet et al.	8,329,680	B2	12/2012	Evans et al.
7,799,769	B2	9/2010	White	8,337,814	B2	12/2012	Osbakken
7,815,936	B2	10/2010	Hasenzahl	8,344,007	B2	1/2013	Chui
7,815,949	B2	10/2010	Cohen	8,349,820	B2	1/2013	Zeun et al.
7,829,115	B2	11/2010	Besins et al.	8,353,863	B2	1/2013	Imran
7,829,116	B2	11/2010	Frye	8,357,723	B2	1/2013	Satyam
RE42,012	E	12/2010	Deaver et al.	8,361,995	B2	1/2013	Schramm
7,850,992	B2	12/2010	Hwang, II	8,362,091	B2	1/2013	Besonov
7,854,753	B2	12/2010	Kraft	8,372,424	B2	2/2013	Berry
7,858,607	B2	12/2010	Mamchur	8,372,806	B2	2/2013	Bragagna
RE42,072	E	1/2011	Deaver et al.	8,377,482	B2	2/2013	Laurie
7,862,552	B2	1/2011	McIntyre et al.	8,377,994	B2	2/2013	Drechsler
7,867,990	B2	1/2011	Schultz et al.	8,394,759	B2	3/2013	Barathur
7,871,643	B2	1/2011	Lizio	8,415,332	B2	4/2013	Reape
7,879,830	B2	2/2011	Wiley	8,420,111	B2	4/2013	Hermismeyer
7,884,093	B2	2/2011	Creasy et al.	8,435,561	B2	5/2013	Besins et al.
7,925,519	B2	4/2011	Greene	8,435,972	B2	5/2013	Sayeed
7,939,104	B2	5/2011	Barbera et al.	8,449,879	B2	5/2013	Applegate
7,943,602	B2	5/2011	Bunschoten et al.	8,450,108	B2	5/2013	Boyce
7,943,604	B2	5/2011	Coelingh Bennink et al.	8,454,945	B2	6/2013	Narain
				8,455,468	B2	6/2013	Kellermann
				8,461,138	B2	6/2013	Boissonneault
				8,476,252	B2	7/2013	Pickersgill
				8,481,488	B2	7/2013	Carter

## US 10,206,932 B2

Page 5

(56)	<b>References Cited</b>					
	U.S. PATENT DOCUMENTS					
	8,486,374 B2	7/2013	Zlatkis	2002/0058926 A1	5/2002	Rathbone et al.
	8,486,442 B2	7/2013	Yamaji	2002/0064541 A1	5/2002	Lapidot et al.
	8,492,368 B2	7/2013	Lewandowski	2002/0076441 A1	6/2002	Shih et al.
	8,507,467 B2	8/2013	Ueda	2002/0102308 A1	8/2002	Wei et al.
	8,512,693 B2	8/2013	Azevedo	2002/0107230 A1	8/2002	Waldon et al.
	8,512,754 B2	8/2013	Needham	2002/0114803 A1	8/2002	Deaver et al.
	8,518,376 B2	8/2013	Schuz	2002/0119174 A1	8/2002	Gardlik
	8,536,159 B2	9/2013	Zeng	2002/0119198 A1	8/2002	Gao
	8,540,967 B2	9/2013	Trivedi	2002/0132801 A1	9/2002	Heil et al.
	8,541,400 B2	9/2013	Joabsson	2002/0137749 A1	9/2002	Levinson et al.
	8,551,462 B2	10/2013	Marenius	2002/0142017 A1	10/2002	Simonnet
	8,551,508 B2	10/2013	Lee et al.	2002/0151530 A1	10/2002	Leonard et al.
	8,557,281 B2	10/2013	Tuominen	2002/0156394 A1	10/2002	Mehrotra et al.
	8,568,374 B2	10/2013	De Graaff	2002/0169150 A1	11/2002	Pickar
	8,591,951 B2	11/2013	Kohn	2002/0169205 A1	11/2002	Garfield
	8,613,951 B2	12/2013	Troiano	2002/0173510 A1	11/2002	Levinson et al.
	8,633,178 B2	1/2014	Cacace	2002/0193356 A1	12/2002	Van Beek et al.
	8,633,180 B2	1/2014	Zeng	2002/0193758 A1	12/2002	Sandberg
	8,636,787 B2	1/2014	Sabaria	2002/0197286 A1	12/2002	Brandman
	8,636,982 B2	1/2014	Schuz	2003/0003139 A1	1/2003	Gunther
	8,653,129 B2	2/2014	Fein	2003/0004145 A1	1/2003	Leonard
	8,658,627 B2	2/2014	Voskuhl	2003/0007994 A1	1/2003	Bunt et al.
	8,658,628 B2	2/2014	Baucom	2003/0027772 A1	2/2003	Breton
	8,663,681 B2	3/2014	Ahmed et al.	2003/0091620 A1	2/2003	Venkateshwaran
	8,663,692 B1	3/2014	Mueller	2003/0044453 A1	3/2003	Volkel
	8,663,703 B2	3/2014	Moldavski	2003/0049307 A1	3/2003	Gyurik
	8,664,207 B2	3/2014	Zheng	2003/0064097 A1	4/2003	Patel et al.
	8,669,293 B2	3/2014	Sharoni	2003/0064975 A1	4/2003	Koch et al.
	8,679,552 B2	3/2014	Guthery	2003/0072760 A1	4/2003	Sirbasku
	8,694,358 B2	4/2014	Tryfon	2003/0073248 A1	4/2003	Roth et al.
	8,697,127 B2	4/2014	Sah	2003/0073673 A1	4/2003	Hesch
	8,697,710 B2	4/2014	Zeng	2003/0077297 A1 *	4/2003	Chen ..... A61K 9/1617 424/400
	8,703,105 B2	4/2014	Besonov	2003/0078245 A1	4/2003	Bennink et al.
	8,709,385 B2	4/2014	Schuz	2003/0091640 A1	5/2003	Ramanathan et al.
	8,709,451 B2	4/2014	Rapoport	2003/0092691 A1	5/2003	Besse et al.
	8,715,735 B2	5/2014	Funke	2003/0096012 A1	5/2003	Besse et al.
	8,721,331 B2	5/2014	Raghuprasad	2003/0104048 A1	6/2003	Patel et al.
	8,722,021 B2	5/2014	Eini	2003/0109507 A1	6/2003	Beckmann
	8,734,846 B2	5/2014	Hrkach	2003/0113268 A1	6/2003	Buenaflae
	8,735,381 B2	5/2014	Podolski	2003/0114420 A1	6/2003	Salvati et al.
	8,741,336 B2	6/2014	Dipierro	2003/0114430 A1	6/2003	MacLeod et al.
	8,741,373 B2	6/2014	Rao	2003/0124182 A1	7/2003	Shojaei et al.
	8,753,661 B2	6/2014	Gassner	2003/0124191 A1	7/2003	Besse et al.
	8,784,882 B2	7/2014	Mattern	2003/0130558 A1	7/2003	Massara et al.
	8,846,648 B2	9/2014	Bernick et al.	2003/0144258 A1	7/2003	Heil et al.
	8,846,649 B2	9/2014	Bernick et al.	2003/0157157 A1	8/2003	Luo et al.
	8,933,059 B2	1/2015	Bernick et al.	2003/0166509 A1	9/2003	Edwards et al.
	8,987,237 B2	3/2015	Bernick et al.	2003/0170295 A1	9/2003	Yoon
	8,987,238 B2	3/2015	Bernick et al.	2003/0175329 A1	9/2003	Mak
	8,993,548 B2	3/2015	Bernick et al.	2003/0175333 A1	9/2003	Shefer
	8,993,549 B2	3/2015	Bernick et al.	2003/0180352 A1	9/2003	Patel et al.
	9,006,222 B2	4/2015	Bernick et al.	2003/0181353 A1	9/2003	Nyce
	9,012,434 B2	4/2015	Bernick et al.	2003/0181728 A1	9/2003	Salvati et al.
	9,114,145 B2	8/2015	Bernick et al.	2003/0191096 A1	10/2003	Leonard et al.
	9,114,146 B2	8/2015	Bernick et al.	2003/0195177 A1	10/2003	Leonard et al.
	9,180,091 B2	11/2015	Bernick et al.	2003/0215496 A1	11/2003	Patel et al.
	9,248,136 B2	2/2016	Bernick et al.	2003/0219402 A1	11/2003	Rutter
	9,289,382 B2	3/2016	Bernick et al.	2003/0220297 A1	11/2003	Bernstein et al.
	9,301,920 B2	4/2016	Bernick et al.	2003/0224057 A1	12/2003	Martin-Letellier et al.
	2001/0005728 A1	2/2001	Guittard et al.	2003/0224059 A1	12/2003	Lerner et al.
	2001/0009673 A1	7/2001	Gunther	2003/0225047 A1	12/2003	Friedman
	2001/0021816 A1	9/2001	Caillouette	2003/0225048 A1	12/2003	Friedman
	2001/0023261 A1	9/2001	Ryoo	2003/0225050 A1	12/2003	Eichardt et al.
	2001/0027189 A1	10/2001	Bennink et al.	2003/0228686 A1	12/2003	Klausner et al.
	2001/0029357 A1	10/2001	Bunt et al.	2003/0229057 A1	12/2003	Caubel et al.
	2001/0031747 A1	10/2001	de Ziegler et al.	2003/0235596 A1	12/2003	Gao
	2001/0032125 A1	10/2001	Bhan et al.	2003/0236236 A1	12/2003	Chen et al.
	2001/0034340 A1	10/2001	Pickar	2004/0009960 A1	1/2004	Heil et al.
	2001/0053383 A1	12/2001	Sablotsky	2004/0022820 A1	2/2004	Anderson
	2001/0056068 A1	12/2001	Chwalisz et al.	2004/0034001 A1	2/2004	Karara
	2002/0012710 A1	1/2002	Lansky	2004/0037881 A1	2/2004	Guittard et al.
	2002/0026158 A1	2/2002	Rathbone et al.	2004/0039356 A1	2/2004	Maki
	2002/0028788 A1	3/2002	Bunt et al.	2004/0043043 A1	3/2004	Schlyter
	2002/0035070 A1	3/2002	Gardlik	2004/0043943 A1	3/2004	Guittard et al.
	2002/0058648 A1	5/2002	Hammerly	2004/0044080 A1	3/2004	Place et al.
				2004/0048900 A1	3/2004	Flood
				2004/0052824 A1	3/2004	Abou Chacra-Vemet et al.
				2004/0073024 A1	4/2004	Metcalf, III et al.



## US 10,206,932 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

2004/0077605	A1	4/2004	Salvati et al.	2005/0244522	A1	11/2005	Carrara et al.
2004/0077606	A1	4/2004	Salvati et al.	2005/0245902	A1	11/2005	Cornish et al.
2004/0087548	A1	5/2004	Salvati et al.	2005/0250746	A1	11/2005	Iammatteo
2004/0087564	A1	5/2004	Wright	2005/0250750	A1	11/2005	Cummings et al.
2004/0089308	A1	5/2004	Welch	2005/0250753	A1	11/2005	Fink et al.
2004/0092494	A9	5/2004	Dudley	2005/0256028	A1	11/2005	Yun et al.
2004/0092583	A1	5/2004	Shanahan-Prendergast	2005/0266078	A1	11/2005	Jorda et al.
2004/0093261	A1	5/2004	Jain et al.	2005/0266088	A1	12/2005	Frijlink
2004/0097468	A1	5/2004	Wimalawansa	2005/0271597	A1	12/2005	Keith
2004/0101557	A1	5/2004	Gibson et al.	2005/0271598	A1	12/2005	Friedman et al.
2004/0106542	A1	6/2004	Deaver et al.	2005/0272685	A1	12/2005	Hung
2004/0110732	A1	6/2004	Masini	2005/0272712	A1	12/2005	Grubb et al.
2004/0131670	A1	7/2004	Gao	2006/0009428	A1	1/2006	Grubb
2004/0138103	A1	7/2004	Patt	2006/0014728	A1	1/2006	Chwalisz et al.
2004/0142012	A1	7/2004	Bunt et al.	2006/0018937	A1	1/2006	Friedman et al.
2004/0146539	A1	7/2004	Gupta	2006/0019978	A1	1/2006	Balog
2004/0146894	A1	7/2004	Warrington et al.	2006/0020002	A1	1/2006	Salvati et al.
2004/0147578	A1	7/2004	Calvet	2006/0030615	A1	2/2006	Fensome et al.
2004/0161435	A1	8/2004	Gupta	2006/0034889	A1	2/2006	Jo et al.
2004/0176324	A1	9/2004	Salvati et al.	2006/0034904	A1	2/2006	Weimann
2004/0176336	A1	9/2004	Rodriguez	2006/0040904	A1	2/2006	Ahmed et al.
2004/0185104	A1	9/2004	Piao et al.	2006/0051391	A1	3/2006	Dvoskin et al.
2004/0191207	A1	9/2004	Lipari	2006/0052341	A1	3/2006	Cornish et al.
2004/0191276	A1	9/2004	Muni	2006/0069031	A1	3/2006	Loumaye
2004/0198706	A1	10/2004	Carrara et al.	2006/0078618	A1	4/2006	Constantinides
2004/0210280	A1	10/2004	Liedtke	2006/0083778	A1	4/2006	Allison et al.
2004/0213744	A1	10/2004	Lulla et al.	2006/0084704	A1	4/2006	Shih
2004/0219124	A1	11/2004	Gupta	2006/0088580	A1	4/2006	Seibertz
2004/0225140	A1	11/2004	Sciano	2006/0089337	A1	4/2006	Casper et al.
2004/0234606	A1	11/2004	Levine et al.	2006/0093678	A1	5/2006	Chickering, III et al.
2004/0241219	A1	12/2004	Hille	2006/0100180	A1	5/2006	Bohlmann
2004/0243437	A1	12/2004	Grace et al.	2006/0106004	A1	5/2006	Brody et al.
2004/0253319	A1	12/2004	Netke et al.	2006/0110415	A1	5/2006	Gupta
2004/0259817	A1	12/2004	Waldon et al.	2006/0111424	A1	5/2006	Salvati et al.
2004/0266745	A1	12/2004	Schwanitz et al.	2006/0121102	A1	6/2006	Chiang
2005/0003003	A1	1/2005	Deaver	2006/0121626	A1	6/2006	Imrich
2005/0004088	A1	1/2005	Hesch	2006/0134188	A1	6/2006	Podhaisky et al.
2005/0009800	A1	1/2005	Thumbeck et al.	2006/0135619	A1	6/2006	Kick et al.
2005/0014729	A1	1/2005	Pulaski	2006/0165744	A1	7/2006	Anyarambhatla
2005/0020550	A1	1/2005	Latif	2006/0193789	A1	8/2006	Tamarkin
2005/0020552	A1	1/2005	Aschkenasay et al.	2006/0194775	A1	8/2006	Tofovic et al.
2005/0021009	A1	1/2005	Massara et al.	2006/0204557	A1	9/2006	Gupta et al.
2005/0025833	A1	2/2005	Aschkenasay et al.	2006/0233743	A1	10/2006	Kelly
2005/0031651	A1	2/2005	Gervais et al.	2006/0233841	A1	10/2006	Pushpala
2005/0042173	A1	2/2005	Besse et al.	2006/0235037	A1	10/2006	Purandare et al.
2005/0042268	A1	2/2005	Aschkenasay et al.	2006/0240111	A1	10/2006	Fernandez et al.
2005/0048116	A1	3/2005	Straub et al.	2006/0246122	A1	11/2006	Langguth et al.
2005/0054991	A1	3/2005	Paterson	2006/0247216	A1	11/2006	Haj-Yehia
2005/0079138	A1	4/2005	Chickering, III et al.	2006/0247221	A1	11/2006	Coelingh Bennink
2005/0085453	A1	4/2005	Govindarajan	2006/0251581	A1	11/2006	Madenjian
2005/0101579	A1	5/2005	Shippen	2006/0252049	A1	11/2006	Shuler et al.
2005/0113350	A1	5/2005	Duesterberg et al.	2006/0257472	A1	11/2006	Neilsen
2005/0118244	A1	6/2005	Theobald	2006/0275218	A1	12/2006	Besonov
2005/0118272	A1	6/2005	Besse et al.	2006/0275360	A1	12/2006	Ahmed et al.
2005/0129756	A1	6/2005	Podhaisky	2006/0276414	A1	12/2006	Coelingh Bennink
2005/0152956	A1	7/2005	Dudley	2006/0280771	A1	12/2006	Groenewegen et al.
2005/0153946	A1	7/2005	Hirsh et al.	2006/0280797	A1	12/2006	Shoichet et al.
2005/0164977	A1	7/2005	Coelingh Bennink	2006/0280800	A1	12/2006	Nagi et al.
2005/0182105	A1	8/2005	Nirschl et al.	2006/0292223	A1	12/2006	Mc Ilroy
2005/0186141	A1	8/2005	Gonda	2007/0004693	A1	1/2007	Woolfson et al.
2005/0187267	A1	8/2005	Hamann et al.	2007/0004694	A1	1/2007	Woolfson et al.
2005/0192253	A1	9/2005	Salvati et al.	2007/0009559	A1	1/2007	Alosio
2005/0192310	A1	9/2005	Gavai et al.	2007/0009594	A1	1/2007	Grubb
2005/0196434	A1	9/2005	Brierre	2007/0010550	A1	1/2007	McKenzie
2005/0207990	A1	9/2005	Funke et al.	2007/0014839	A1	1/2007	Bracht
2005/0209209	A1	9/2005	Koch et al.	2007/0015698	A1	1/2007	Goldstein
2005/0214384	A1	9/2005	Juturu et al.	2007/0021360	A1	1/2007	Nyce et al.
2005/0220825	A1	10/2005	Funke et al.	2007/0027201	A1	2/2007	McComas et al.
2005/0220900	A1	10/2005	Wuttke	2007/0031491	A1	2/2007	Levine et al.
2005/0222106	A1	10/2005	Bracht	2007/0037780	A1	2/2007	Anigbogu
2005/0228692	A1	10/2005	Hodgdon	2007/0037782	A1	2/2007	Suzuki
2005/0228718	A1	10/2005	Austin	2007/0042038	A1	2/2007	Besse
2005/0239747	A1	10/2005	Yuan	2007/0060589	A1	3/2007	Purandare et al.
2005/0239758	A1	10/2005	Roby	2007/0066628	A1	3/2007	Zhang et al.
2005/0244360	A1	11/2005	Billoni	2007/0066637	A1	3/2007	Zhang et al.
				2007/0066675	A1	3/2007	Zhang et al.
				2007/0078091	A1	4/2007	Hubler
				2007/0088029	A1	4/2007	Balog et al.
				2007/0093548	A1	4/2007	Diffendal et al.

## US 10,206,932 B2

Page 7

## (56) References Cited

## U.S. PATENT DOCUMENTS

2007/0116729	A1	5/2007	Palepu	2009/0004246	A1	1/2009	Woolfson
2007/0116829	A1	5/2007	Prakash et al.	2009/0010968	A1	1/2009	Peyrot
2007/0128263	A1	6/2007	Wall	2009/0011041	A1	1/2009	Musaeva
2007/0154533	A1	7/2007	Dudley	2009/0017120	A1	1/2009	Brisco
2007/0167418	A1	7/2007	Ferguson	2009/0022683	A1	1/2009	Park
2007/0178166	A1	8/2007	Bernstein et al.	2009/0047357	A1	2/2009	Tomohira
2007/0184558	A1	8/2007	Roth et al.	2009/0053294	A1	2/2009	Prendergast
2007/0185068	A1	8/2007	Ferguson	2009/0060982	A1	3/2009	Ron et al.
2007/0190022	A1	8/2007	Chiao	2009/0060997	A1	3/2009	Seitz
2007/0191319	A1	8/2007	Ke et al.	2009/0068118	A1	3/2009	Eini et al.
2007/0196415	A1	8/2007	Houston	2009/0074859	A1	3/2009	Patel
2007/0196433	A1	8/2007	Ron et al.	2009/0081206	A1	3/2009	Leibovitz
2007/0207225	A1	9/2007	Squadrito	2009/0081278	A1	3/2009	De Graaff et al.
2007/0225281	A1	9/2007	Zhang et al.	2009/0081303	A1	3/2009	Savoir et al.
2007/0232574	A1	10/2007	Bernard	2009/0092656	A1	4/2009	Klamerus et al.
2007/0238713	A1	10/2007	Gast et al.	2009/0093440	A1	4/2009	Murad
2007/0243229	A1	10/2007	Smith et al.	2009/0098069	A1	4/2009	Vacca
2007/0248658	A1	10/2007	Bracht	2009/0099106	A1	4/2009	Phiasivongsa et al.
2007/0254858	A1	11/2007	Cronk	2009/0099149	A1	4/2009	Kresecvic
2007/0255197	A1	11/2007	Wilkins	2009/0130029	A1	5/2009	Tamarkin
2007/0264309	A1	11/2007	Chollet et al.	2009/0131385	A1	5/2009	Voskuhl
2007/0264345	A1	11/2007	Eros et al.	2009/0137478	A1	5/2009	Bernstein et al.
2007/0264349	A1	11/2007	Lee et al.	2009/0137538	A1	5/2009	Klamerus et al.
2007/0286819	A1	12/2007	DeVries et al.	2009/0143344	A1	6/2009	Chang
2007/0287688	A1	12/2007	Chan	2009/0164341	A1	6/2009	Sunvold et al.
2007/0287789	A1	12/2007	Jones et al.	2009/0175799	A1	7/2009	Tamarkin
2007/0292359	A1	12/2007	Schuz	2009/0181088	A1	7/2009	Song et al.
2007/0292387	A1	12/2007	Jon et al.	2009/0186081	A1	7/2009	Slot
2007/0292461	A1	12/2007	Danziger	2009/0197843	A1	8/2009	Notelovitz
2007/0292493	A1	12/2007	Brierre	2009/0203658	A1	8/2009	Rose
2007/0298089	A1	12/2007	Yoshinaga	2009/0214474	A1	8/2009	Jennings
2008/0026035	A1	1/2008	Chollet et al.	2009/0227025	A1	9/2009	Nichols et al.
2008/0026040	A1	1/2008	Guzman	2009/0227550	A1	9/2009	Mattern
2008/0026062	A1	1/2008	Farr et al.	2009/0232897	A1	9/2009	Sahoo et al.
2008/0038219	A1	2/2008	Carlson	2009/0258096	A1	10/2009	Cohen
2008/0038350	A1	2/2008	Gerecke et al.	2009/0264395	A1	10/2009	Creasy
2008/0039405	A1	2/2008	Joseph	2009/0269403	A1	10/2009	Shaked et al.
2008/0050317	A1	2/2008	Besonov	2009/0285772	A1	11/2009	Phiasivongsa et al.
2008/0051351	A1	2/2008	Ghisalberti	2009/0285869	A1	11/2009	Trimble
2008/0063607	A1	3/2008	Berman	2009/0318558	A1	12/2009	Kim et al.
2008/0069779	A1	3/2008	Schuz	2009/0324714	A1	12/2009	Kresecvic
2008/0069791	A1	3/2008	Beissert	2009/0325916	A1	12/2009	Zhang et al.
2008/0085877	A1	4/2008	Bortz	2010/0008985	A1	1/2010	Vermeulen
2008/0095831	A1	4/2008	McGraw	2010/0028360	A1	2/2010	Atwood
2008/0095838	A1	4/2008	Abou Chacra-Vemet	2010/0034838	A1	2/2010	Staniforth
2008/0119537	A1	5/2008	Zhang et al.	2010/0034880	A1	2/2010	Sintov
2008/0125402	A1	5/2008	Dilberti	2010/0040671	A1	2/2010	Ahmed et al.
2008/0138379	A1	6/2008	Jennings-Spring	2010/0048523	A1	2/2010	Bachman et al.
2008/0138390	A1	6/2008	Gricenko	2010/0055138	A1	3/2010	Jacobs
2008/0139392	A1	6/2008	Yuan	2010/0074959	A1	3/2010	Hansom et al.
2008/0145423	A1	6/2008	Khan et al.	2010/0086501	A1	4/2010	Chang
2008/0153789	A1	6/2008	Dmowski	2010/0086599	A1	4/2010	Huempel et al.
2008/0175814	A1	7/2008	Phiasivongsa et al.	2010/0092568	A1	4/2010	Lerner et al.
2008/0175905	A1	7/2008	Blksh	2010/0105071	A1	4/2010	Laufer et al.
2008/0175908	A1	7/2008	Blksh	2010/0119585	A1	5/2010	Hille et al.
2008/0188829	A1	8/2008	Creasy	2010/0129320	A1	5/2010	Phiasivongsa et al.
2008/0206156	A1	8/2008	Cronk	2010/0136105	A1	6/2010	Chen et al.
2008/0206159	A1	8/2008	Schuz	2010/0137265	A1	6/2010	Leonard
2008/0206161	A1	8/2008	Tamarkin et al.	2010/0137271	A1	6/2010	Chen et al.
2008/0214512	A1	9/2008	Seitz	2010/0143420	A1	6/2010	Lee
2008/0220069	A1	9/2008	Allison	2010/0143481	A1	6/2010	Shenoy
2008/0226698	A1	9/2008	Beste	2010/0150993	A1	6/2010	Theobald
2008/0227763	A1	9/2008	Paris	2010/0152144	A1	6/2010	Hermesmeier
2008/0234199	A1	9/2008	Katamreddy	2010/0168228	A1	7/2010	Bose et al.
2008/0234240	A1	9/2008	Duesterberg	2010/0183723	A1	7/2010	Laurent-Applegate et al.
2008/0255078	A1	10/2008	Katamreddy	2010/0184736	A1	7/2010	Coelingh Bennink et al.
2008/0255089	A1	10/2008	Katamreddy	2010/0190758	A1	7/2010	Fauser et al.
2008/0261931	A1	10/2008	Stenlof	2010/0204326	A1	8/2010	D Souza
2008/0113953	A1	12/2008	DeVries et al.	2010/0210994	A1	8/2010	Zarif
2008/0114050	A1	12/2008	Fensome et al.	2010/0221195	A1	9/2010	Ziv
2008/0299220	A1	12/2008	Tamarkin et al.	2010/0227797	A1	9/2010	Danielsson
2008/0306036	A1	12/2008	Katamreddy	2010/0240626	A1	9/2010	Kulkarni et al.
2008/0312197	A1	12/2008	Rodriguez	2010/0247482	A1	9/2010	Chen
2008/0312198	A1	12/2008	Rodriguez	2010/0247632	A1	9/2010	Dong et al.
2008/0319078	A1	12/2008	Katamreddy	2010/0247635	A1	9/2010	Schmidt
				2010/0255085	A1	10/2010	Liu et al.
				2010/0273730	A1	10/2010	Hsu
				2010/0278759	A1	11/2010	Murad
				2010/0279988	A1	11/2010	Setiawan



## US 10,206,932 B2

Page 8

(56)	<b>References Cited</b>					
	U.S. PATENT DOCUMENTS					
2010/0291191	A1	11/2010	Lapitsky	2012/0128625	A1	5/2012 Shalwitz et al.
2010/0292199	A1	11/2010	Leverd	2012/0128654	A1	5/2012 Terpstra
2010/0303825	A9	12/2010	Sirbasku	2012/0128683	A1	5/2012 Shantha
2010/0312137	A1	12/2010	Gilmour et al.	2012/0128733	A1	5/2012 Perrin
2010/0316724	A1	12/2010	Whitfield et al.	2012/0128777	A1	5/2012 Keck et al.
2010/0322884	A1	12/2010	Wilkins	2012/0129773	A1	5/2012 Geier
2010/0330168	A1	12/2010	Gicquel et al.	2012/0129819	A1	5/2012 Vancaillie
2011/0028439	A1	2/2011	Witt-Enderby et al.	2012/0136013	A1	5/2012 Wennogle
2011/0039814	A1	2/2011	Ross	2012/0142645	A1	6/2012 Marx
2011/0053845	A1	3/2011	Levine et al.	2012/0148670	A1	6/2012 Lee
2011/0066473	A1	3/2011	Bernick et al.	2012/0149748	A1	6/2012 Shanler et al.
2011/0076775	A1	3/2011	Stewart et al.	2012/0172343	A1	7/2012 Schuermann
2011/0076776	A1	3/2011	Stewart et al.	2012/0184515	A1	7/2012 Schwede
2011/0086825	A1	4/2011	Chatroux	2012/0231052	A1	9/2012 Brinton
2011/0087192	A1	4/2011	Uhland	2012/0232011	A1	9/2012 Kneissel
2011/0091555	A1	4/2011	De Luigi Bruschi et al.	2012/0232042	A1	9/2012 Krenz
2011/0098258	A1	4/2011	Canet	2012/0263679	A1	10/2012 Wallace
2011/0098631	A1	4/2011	McIntyre et al.	2012/0269721	A1	10/2012 Weng et al.
2011/0104268	A1	5/2011	Segot	2012/0269878	A2	10/2012 Cantor et al.
2011/0104289	A1	5/2011	Savoir Vilboeuf et al.	2012/0277249	A1	11/2012 Tarrand
2011/0130372	A1	6/2011	Marliani	2012/0277727	A1	11/2012 Doshi
2011/0135719	A1	6/2011	Besins et al.	2012/0283671	A1	11/2012 Shibata et al.
2011/0142945	A1	6/2011	Chen	2012/0295911	A1	11/2012 Mannion
2011/0152840	A1	6/2011	Lee	2012/0301517	A1	11/2012 Warner
2011/0158920	A1	6/2011	Fisher	2012/0301538	A1	11/2012 Latere
2011/0171140	A1	7/2011	Illum	2012/0302535	A1	11/2012 Caufriez
2011/0182997	A1	7/2011	Lewis et al.	2012/0316130	A1	12/2012 Hendrix
2011/0190201	A1	8/2011	Wood, Jr.	2012/0316496	A1	12/2012 Horres
2011/0195031	A1	8/2011	Du	2012/0321579	A1	12/2012 Edelson
2011/0195114	A1	8/2011	Carrara et al.	2012/0322779	A9	12/2012 Voskuhl
2011/0195944	A1	8/2011	Mura et al.	2012/0328549	A1	12/2012 Edelson
2011/0217341	A1	9/2011	Sah	2012/0329738	A1	12/2012 Liu
2011/02338003	A1	9/2011	Karabelas	2013/0004619	A1	1/2013 Goh
2011/0244043	A1	10/2011	Wang	2013/0011342	A1	1/2013 Hazot
2011/0250256	A1	10/2011	Hyun Oh	2013/0017239	A1	1/2013 Fernandez
2011/0250259	A1	10/2011	Buckman	2013/0022674	A1	1/2013 Dudley et al.
2011/0250274	A1	10/2011	Shaked et al.	2013/0023505	A1	1/2013 Garfield
2011/0256092	A1	10/2011	Phiasivongsa et al.	2013/0023823	A1	1/2013 Volland
2011/0262373	A1	10/2011	Umbert Millet	2013/0028850	A1	1/2013 Hazot
2011/0262494	A1	10/2011	Achleitner et al.	2013/0029947	A1	1/2013 Nachaegari et al.
2011/0268665	A1	11/2011	Tamarkin et al.	2013/0029957	A1	1/2013 Venkateshwaran
2011/0275584	A1	11/2011	Volkman	2013/0045266	A1	2/2013 Kang
2011/0281832	A1	11/2011	Wennogle	2013/0045953	A1	2/2013 Grenier
2011/0287094	A1	11/2011	Penhasi	2013/0059795	A1	3/2013 Lo
2011/0293720	A1	12/2011	General et al.	2013/0064897	A1	3/2013 Binay
2011/0294738	A1	12/2011	Kuliopulos	2013/0072466	A1	3/2013 Choi
2011/0300167	A1	12/2011	Covic	2013/0084257	A1	4/2013 Ishida
2011/0301087	A1	12/2011	McBride	2013/0085123	A1	4/2013 Zhao
2011/0306579	A1	12/2011	Stein	2013/0089574	A1	4/2013 Stock
2011/0311592	A1	12/2011	Birbara	2013/0090318	A1	4/2013 Gainer
2011/0312927	A1	12/2011	Nachaegari et al.	2013/0102781	A1	4/2013 Ely
2011/0312928	A1	12/2011	Nachaegari et al.	2013/0108551	A1	5/2013 Gruell
2011/0318405	A1	12/2011	Erwin	2013/0116215	A1	5/2013 Lleo
2011/0318431	A1	12/2011	Gulati	2013/0116222	A1	5/2013 Altomari
2012/0009276	A1	1/2012	De Groote	2013/0122051	A1	5/2013 Gullapalli
2012/0015350	A1	1/2012	Nabatiyan et al.	2013/0123175	A1	5/2013 McKee
2012/0021041	A1	1/2012	Rossi	2013/0123220	A1	5/2013 Queiroz
2012/0028888	A1	2/2012	Janz	2013/0123351	A1	5/2013 Dewitt
2012/0028910	A1	2/2012	Takruri	2013/0129818	A1	5/2013 Bernick et al.
2012/0028936	A1	2/2012	Popova	2013/0131027	A1	5/2013 Schmitz
2012/0045532	A1	2/2012	Cohen	2013/0131028	A1	5/2013 Snyder
2012/0046264	A1	2/2012	Lieb	2013/0131029	A1	5/2013 Baltussen
2012/0046518	A1	2/2012	Yoakum	2013/0149314	A1	6/2013 Bullerdiek
2012/0052077	A1	3/2012	Truitt, III et al.	2013/0164225	A1	6/2013 Besonov
2012/0058171	A1	3/2012	Zeeman	2013/0164346	A1	6/2013 Son
2012/0058962	A1	3/2012	Sparrow	2013/0165744	A1	6/2013 Carson
2012/0058979	A1	3/2012	Auspitz	2013/0178452	A1	7/2013 King
2012/0064135	A1	3/2012	Harms	2013/0183254	A1	7/2013 Cochran
2012/0065179	A1	3/2012	Andersson	2013/0183325	A1	7/2013 Sforzini
2012/0065221	A1	3/2012	Babul	2013/0189193	A1	7/2013 Besonov
2012/0087872	A1	4/2012	Schuz	2013/0189196	A1	7/2013 Tamarkin
2012/0101073	A1	4/2012	Mannion	2013/0189230	A1	7/2013 Van D Kooy
2012/0121517	A1	5/2012	Kim	2013/0189368	A1	7/2013 Mosqueira
2012/0121692	A1	5/2012	Fang	2013/0210709	A1	8/2013 Covic
2012/0122829	A1	5/2012	Masini	2013/0216550	A1	8/2013 Penninger
				2013/0216596	A1	8/2013 Fernandez
				2013/0224177	A1	8/2013 Kim
				2013/0224257	A1	8/2013 Sah
				2013/0224268	A1	8/2013 Jaikaria

## US 10,206,932 B2

Page 9

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2013/0224300 A1 8/2013 Maggio  
 2013/0225412 A1 8/2013 Sardari Lodriche  
 2013/0225542 A1 8/2013 Frick  
 2013/0226113 A1 8/2013 Langguth  
 2013/0243696 A1 9/2013 Wang  
 2013/0245253 A1 9/2013 Mook  
 2013/0245570 A1 9/2013 Jackson  
 2013/0261096 A1 10/2013 Merian  
 2013/0266645 A1 10/2013 Schoenecker  
 2013/0267485 A1 10/2013 Da Silva Maia Filho  
 2013/0273167 A1 10/2013 Kim  
 2013/0274211 A1 10/2013 Prusthy  
 2013/0280213 A1 10/2013 Voskuhl  
 2013/0316374 A1 11/2013 Menon  
 2013/0317065 A1 11/2013 Seto  
 2013/0317315 A1 11/2013 Tsang  
 2013/0324565 A1 12/2013 Zhao  
 2013/0331363 A1 12/2013 Zhao  
 2013/0338122 A1 12/2013 Bernick et al.  
 2013/0338123 A1 12/2013 Bernick et al.  
 2013/0338124 A1 12/2013 Zhao  
 2013/0345187 A1 12/2013 Rodriguez Oquendo  
 2014/0018335 A1 1/2014 Seto  
 2014/0024590 A1 1/2014 Taylor  
 2014/0031289 A1 1/2014 Kim  
 2014/0031323 A1 1/2014 Perez  
 2014/0066416 A1 3/2014 Leunis  
 2014/0072531 A1 3/2014 Oh  
 2014/0079686 A1 3/2014 Prouty  
 2014/0088051 A1 3/2014 Bernick et al.  
 2014/0088058 A1 3/2014 Maurizio  
 2014/0088059 A1 3/2014 Santha  
 2014/0094426 A1 4/2014 Drummond  
 2014/0094440 A1 4/2014 Bernick et al.  
 2014/0094441 A1 4/2014 Bernick et al.  
 2014/0099362 A1 4/2014 Bernick et al.  
 2014/0100159 A1 4/2014 Conrad  
 2014/0100204 A1 4/2014 Bernick et al.  
 2014/0100205 A1 4/2014 Bernick et al.  
 2014/0100206 A1 4/2014 Cacace  
 2014/0113889 A1 4/2014 Haine  
 2014/0127185 A1 5/2014 Sayeed  
 2014/0127280 A1 5/2014 Jukarainen  
 2014/0127308 A1 5/2014 Opara  
 2014/0128798 A1 5/2014 Malanchin  
 2014/0148491 A1 5/2014 Valia et al.  
 2014/0186332 A1 7/2014 Ezrin  
 2014/0187487 A1 7/2014 Shoichet  
 2014/0193523 A1 7/2014 Henry  
 2014/0194396 A1 7/2014 Wennogle  
 2014/0206616 A1 7/2014 Ko et al.  
 2014/0213565 A1 7/2014 Bernick et al.  
 2014/0329783 A1 11/2014 Bernick et al.  
 2014/0370084 A1 12/2014 Bernick et al.  
 2014/0371182 A1 12/2014 Bernick et al.  
 2014/0371183 A1 12/2014 Bernick et al.  
 2014/0371184 A1 12/2014 Bernick et al.  
 2014/0371185 A1 12/2014 Bernick et al.  
 2015/0031654 A1 1/2015 Amadio  
 2015/0045335 A1 2/2015 Bernick et al.  
 2015/0133421 A1 5/2015 Bernick et al.  
 2015/0164789 A1 6/2015 Bernick et al.  
 2015/0224117 A1 8/2015 Bernick et al.  
 2015/0224118 A1 8/2015 Bernick et al.  
 2015/0302435 A1 10/2015 Bernick et al.  
 2015/0342963 A1 12/2015 Bernick et al.  
 2015/0352126 A1 12/2015 Bernick et al.  
 2015/0359737 A1 12/2015 Bernick et al.  
 2016/0030449 A1 2/2016 Persicaner et al.  
 2016/0213685 A1 7/2016 Bernick et al.  
 2017/0056418 A1 3/2017 Thorsteinsson et al.  
 2017/0216310 A1 8/2017 Mirkin et al.  
 2017/0281645 A1 10/2017 Shadiack et al.

2017/0281646 A1 10/2017 Inskip et al.  
 2017/0281647 A1 10/2017 Shadiack et al.  
 2017/0281776 A1 10/2017 Shadiack et al.

## FOREIGN PATENT DOCUMENTS

CN 102258455 A 11/2011  
 EP 0275716 A1 7/1988  
 EP 0279977 A2 8/1988  
 EP 0622075 A1 11/1994  
 EP 0785211 A1 7/1997  
 EP 0785212 A1 7/1997  
 EP 0811381 A1 12/1997  
 EP 0904064 A1 3/1999  
 EP 1094781 B1 7/2008  
 EP 2191833 A1 6/2010  
 GB 452238 A 8/1936  
 GB 720561 A 12/1954  
 GB 848881 A 9/1960  
 GB 874368 A 8/1961  
 GB 1589946 A 5/1981  
 IN 2005KOL00053 8/2005  
 IN 216026 3/2008  
 IN 244217 11/2010  
 JP H4-503810 9/1990  
 JP H2-264725 A 10/1990  
 WO 1990011064 10/1990  
 WO 1993017686 9/1993  
 WO 1994022426 10/1994  
 WO 1995030409 11/1995  
 WO 1996009826 4/1996  
 WO 1996019975 7/1996  
 WO 1996030000 10/1996  
 WO 1997005491 2/1997  
 WO 1997043989 11/1997  
 WO 1998010293 3/1998  
 WO 1998032465 7/1998  
 WO 1998051280 11/1998  
 WO 1999022680 A1 5/1999  
 WO 1999032072 7/1999  
 WO 1999039700 8/1999  
 WO 1999042109 8/1999  
 WO 1999043304 9/1999  
 WO 1999048477 9/1999  
 WO 1999053910 10/1999  
 WO 1999062497 A1 12/1999  
 WO 1999063974 12/1999  
 WO 2000001351 1/2000  
 WO 2000006175 2/2000  
 WO 2000038659 6/2000  
 WO 2000045795 8/2000  
 WO 2000050007 8/2000  
 WO 2000059577 10/2000  
 WO 2000076522 12/2000  
 WO 2001037808 5/2001  
 WO 2001054699 8/2001  
 WO 2001060325 8/2001  
 WO 2001087276 11/2001  
 WO 2001091757 12/2001  
 WO 2002007700 1/2002  
 WO 2002011768 2/2002  
 WO 2002022132 3/2002  
 WO 2002040008 5/2002  
 WO 2002041878 5/2002  
 WO 2002053131 7/2002  
 WO 2002078602 10/2002  
 WO 2002078604 10/2002  
 WO 2003028667 4/2003  
 WO 2003041718 5/2003  
 WO 2003041741 5/2003  
 WO 2003068186 8/2003  
 WO 2003077923 9/2003  
 WO 2003082254 10/2003  
 WO 2003092588 11/2003  
 WO 2004014397 A1 2/2004  
 WO 2004014432 2/2004  
 WO 2004017983 3/2004  
 WO 2004032897 4/2004  
 WO 2004052336 6/2004

## US 10,206,932 B2

Page 10

(56)

## References Cited

## FOREIGN PATENT DOCUMENTS

WO	2004054540	7/2004
WO	2004080413	9/2004
WO	2004110408 A2	12/2004
WO	2005027911	3/2005
WO	2005030175	4/2005
WO	2007076144 A2	7/2005
WO	2005081825	9/2005
WO	2005087194	9/2005
WO	2005087199	9/2005
WO	2005105059	11/2005
WO	2005115335	12/2005
WO	2005120470	12/2005
WO	2005120517	12/2005
WO	2006013369	2/2006
WO	2006034090	3/2006
WO	2006036899	4/2006
WO	2006053172	5/2006
WO	2006105615	10/2006
WO	2006113505	10/2006
WO	2006138686	12/2006
WO	2006138735	12/2006
WO	2007045027	4/2007
WO	2007103294	9/2007
WO	2007120868	10/2007
WO	2007123790	11/2007
WO	2007124250	11/2007
WO	2007144151	12/2007
WO	2008049516	5/2008
WO	2008152444	12/2008
WO	2009002542	12/2008
WO	2009036311	3/2009
WO	2009040818	4/2009
WO	2009069006	6/2009
WO	2009098072	8/2009
WO	2009133352	11/2009
WO	2010033188	3/2010
WO	2010146872	12/2010
WO	2011000210	1/2011
WO	2011073995	6/2011
WO	2011120084	10/2011
WO	2011128336	10/2011
WO	2012009778	1/2012
WO	2012024361	2/2012
WO	2012055814 A1	5/2012
WO	2012055840 A1	5/2012
WO	2012065740	5/2012
WO	2012098090 A1	7/2012
WO	2012116277 A1	8/2012
WO	2012118563 A2	9/2012
WO	2012120365 A1	9/2012
WO	2012127501 A2	9/2012
WO	2012156561 A1	11/2012
WO	2012156822 A1	11/2012
WO	2012158483 A2	11/2012
WO	2012166909 A1	12/2012
WO	2012170578 A1	12/2012
WO	2013011501 A1	1/2013
WO	2013025449 A1	2/2013
WO	2013028639 A1	2/2013
WO	2013035101 A1	3/2013
WO	2013044067 A1	3/2013
WO	2013045404 A2	4/2013
WO	2013059285 A1	4/2013
WO	2013063279 A1	5/2013
WO	2013064620 A1	5/2013
WO	2013071281 A1	5/2013
WO	2013078422 A2	5/2013
WO	2013088254	6/2013
WO	2013102665 A1	7/2013
WO	2013106437 A1	7/2013
WO	2013112947 A1	8/2013
WO	2013113690	8/2013
WO	2013124415 A1	8/2013
WO	2013127727 A1	9/2013
WO	2013127728 A1	9/2013

WO	2013144356 A1	10/2013
WO	2013149258 A2	10/2013
WO	2013158454 A2	10/2013
WO	2013170052 A1	11/2013
WO	2013178587 A1	12/2013
WO	2013181449 A1	12/2013
WO	2013192248	12/2013
WO	2013192249	12/2013
WO	2013192250	12/2013
WO	2013192251	12/2013
WO	2014001904 A1	1/2014
WO	2014004424 A1	1/2014
WO	2014009434 A1	1/2014
WO	2014018569 A1	1/2014
WO	2014018570 A1	1/2014
WO	2014018571 A2	1/2014
WO	2014018856 A1	1/2014
WO	2014018932 A2	1/2014
WO	2014031958 A1	2/2014
WO	2014041120 A1	3/2014
WO	2014052792 A1	4/2014
WO	2014056897 A1	4/2014
WO	2014066442 A2	5/2014
WO	2014074846 A1	5/2014
WO	2014076231 A1	5/2014
WO	2014076569 A2	5/2014
WO	2014081598 A1	5/2014
WO	2014086739 A1	6/2014
WO	2014093114 A1	6/2014
WO	2014104784 A1	7/2014
WO	2015179782 A1	11/2015
WO	2016018993 A1	2/2016

## OTHER PUBLICATIONS

U.S. Appl. No. 14/099,545, filed Dec. 6, 2013, U.S. Pat. No. 8,846,648, Sep. 30, 2014.

U.S. Appl. No. 14/099,562, filed Dec. 6, 2013, U.S. Pat. No. 8,987,237, Mar. 24, 2015.

U.S. Appl. No. 14/099,571, filed Dec. 6, 2013, U.S. Pat. No. 8,846,649, Sep. 30, 2014.

U.S. Appl. No. 14/099,582, filed Dec. 6, 2013, U.S. Pat. No. 9,012,434, Apr. 21, 2015.

U.S. Appl. No. 14/099,598, filed Dec. 6, 2013, U.S. Pat. No. 8,987,238, Mar. 24, 2015.

U.S. Appl. No. 14/099,612, filed Dec. 6, 2013, U.S. Pat. No. 8,933,059, Jan. 13, 2015.

U.S. Appl. No. 14/099,623, filed Dec. 6, 2013, U.S. Pat. No. 9,006,222, Apr. 14, 2015.

U.S. Appl. No. 14/106,655, filed Dec. 13, 2013.

U.S. Appl. No. 14/125,554, filed Jan. 25, 2013, U.S. Pat. No. 9,248,136, Feb. 2, 2016.

U.S. Appl. No. 14/136,048, filed Dec. 20, 2013, U.S. Pat. No. 9,180,091, Nov. 10, 2015.

U.S. Appl. No. 14/475,814, filed Sep. 3, 2014, U.S. Pat. No. 8,993,548, Mar. 31, 2015.

U.S. Appl. No. 14/475,864, filed Sep. 3, 2014, U.S. Pat. No. 8,993,549, Mar. 31, 2015.

U.S. Appl. No. 14/475,946, filed Sep. 3, 2014, U.S. Pat. No. 9,114,145, Aug. 25, 2015.

U.S. Appl. No. 14/476,040, filed Sep. 3, 2014, U.S. Pat. No. 9,114,146, Aug. 25, 2015.

U.S. Appl. No. 14/512,046, filed Oct. 10, 2014.

U.S. Appl. No. 14/521,002, filed Oct. 22, 2014.

U.S. Appl. No. 14/521,230, filed Oct. 22, 2014.

U.S. Appl. No. 14/624,051, filed Feb. 17, 2015, U.S. Pat. No. 9,289,382, Mar. 22, 2016.

U.S. Appl. No. 14/649,818, filed Jun. 18, 2013.

U.S. Appl. No. 14/690,913, filed Apr. 20, 2015.

U.S. Appl. No. 14/690,955, filed Apr. 20, 2015.

U.S. Appl. No. 14/812,179, filed Jul. 29, 2015.

U.S. Appl. No. 14/830,398, filed Aug. 19, 2015.

U.S. Appl. No. 15/090,493, filed Apr. 4, 2016.

U.S. Appl. No. 15/372,385, filed Dec. 7, 2016.

U.S. Appl. No. 15/420,019, filed Jan. 30, 2017.

U.S. Appl. No. 15/475,052, filed Mar. 30, 2017.

## US 10,206,932 B2

Page 11

(56)

## References Cited

## OTHER PUBLICATIONS

- U.S. Appl. No. 15/475,068, filed Mar. 30, 2017.  
 U.S. Appl. No. 15/832,750, filed Dec. 5, 2017.  
 U.S. Appl. No. 15/832,757, filed Dec. 5, 2017.  
 U.S. Appl. No. 15/893,542, filed Feb. 9, 2018.  
 U.S. Appl. No. 15/893,546, filed Feb. 9, 2018.  
 U.S. Appl. No. 15/893,550, filed Feb. 9, 2018.  
 Abbas et al., Regression of endometrial implants treated with vitamin D3 in a rat model of endometriosis, *European J of Pharma*, 715 (2013) 72-75, Elsevier.  
 Abitec, CapmulMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.  
 Abitec, CapmulMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.  
 Abitec, CapmulMCM, Saftey Data Sheet, 2011, Janesville, WI.  
 Abitec, CapmulMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.  
 Abitec, CapmulPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.  
 Abitec, Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2013, 2 pages.  
 Acarturk, Fusun, Mucoadhesive Vaginal Drug Delivery System, Recent Patents on Drug Delivery & Formulation, 2009, vol. 3, pp. 193-195.  
 Alabi, K. A., et al., Analysis of Fatty Acid Composition of Thevetia peruviana and Hura crepitans Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.  
 Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.  
 Alvarez et al., Ectopic uterine tissue as a chronic pain generator, *Neuroscience*, Dec. 6, 2012, 225: 269-272.  
 Application Note FT-IR: JI-Ap-FT0508-008, CD spectra of pharmaceuticals substances—Steroids (2), JASCO International Co., Ltd., 2 pages.  
 Araya-Sibljá et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.  
 Araya-Sibljá, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHn), *Scanning* vol. 35 pp. 213-221, 2013, Wiley Period., Inc.  
 Araya-Sibljá, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., SciFinder, 2014, American Chemical Society & US Natl. Lib. of Med.  
 Araya-Sibljá, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.  
 Araya-Sibljá, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.  
 Archer et al., Effects of ospemifene on the female reproductive and urinary tracts: translation from preclinical models into clinical evidence, *Menopause: The Journal of the North American Menopause Society*, vol. 22, No. 77, pp. 1-11 (2015).  
 Archer et al., Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study, *Advances in Therapy®*, vol. 9 No. 1, Jan./Feb. 1992.  
 Ashburn et al., Cardiovascular, Hepatic and Renal Lesions in Mice Receiving Cortisone, Estrone and Progesterone, *Yale J Biology and Medicine*, vol. 35, Feb. 1963, pp. 329-340.  
 Azeem, Adnan et al., Microemulsions as a Surrogate Carrier for Dermal Drug Delivery, *Drug Development and Industrial Pharmacy*, May 2000, vol. 35, No. 5, pp. 525-547 (abstract only). <http://informahealthcare.com/doi/abs/10.1080/03639040802448646>.  
 Azure Pharma, Inc., ELESTRIN™—Estradiol Gel, Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=11885>, 26 pages, Aug. 2009.  
 Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.  
 Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, *Steroids*, vol. 46(6), pp. 967-974, Dec. 1985.  
 Barnett, Steven M, Pressure-tuning infared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , *Vibrational Spectroscopy* 8, Elsevier, pp. 263, 1995.  
 Bartosova, Transdermal Drug Delivery In Vitro Using Diffusion Cells, *Current Medicinal Chemistry*, 2012, 19, 4671-4677, Bentham Science Publishers.  
 Benbow et al., Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus during Rat Pregnancy, *Biology of Reproduction* 52, 1327-1333 (1995).  
 Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, *Bollettino Chimico Farmaceutico*, vol. 122(1) pp. 20-26, 1983 SciFinder.  
 Bhavnani Bhagu R. et al., "Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy," *J Clin Endocrinol Metab*, Mar. 2012, 97(3):756-759.  
 Bhavnani et al., Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ERs) ERα and ERβ, *Endocrinology*, Oct. 2008, 149(10):4857-4870.  
 Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.  
 Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.  
 BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-106-S2.pdf>.  
 Blake et al., Single and multidose pharmacokinetic study of a vaginal micronized progesterone insert (Endometrin) compared with vaginal gel in healthy reproductive aged female subjects, *Fertility and Sterility* vol. 94, No. 4, Sep. 2010, Elsevier.  
 Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, *Acta Pharm. Jugosl.*, vol. 40 pp. 71-94, 1990.  
 Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.  
 British Pharmacopoeia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/bp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index> [Feb. 3, 2014 1:37:50 PM].  
 Burry, Kenneth A, Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, *Am J Obstet Gynecol*, vol. 180(6) part 1, pp. 1504-1511, 1999.  
 Busetta, Par Bernard, Structure Cristalline et Molculaire de l'Oestradiol Hemihydrate, *Acta Cryst.*, B28 pp. 560, 1972, Bis(dimethyl-*o*-thiophenylarsine)palladium(II).  
 Busetta, Par Bernard, Structure Cristalline et Molculaire du Complexe Oestradiol-Propanol, *Acta Cryst.*, B28 pp. 1349, 1972, J.A. Kanters and J. Kroon.  
 Campsteyn, Par H, et al., Structure Cristalline et Molculaire de la Progesterone C21H30O2, *Acta Cryst.*, B28 pp. 3032-3042, 1972.  
 Castelo-Branco Camil et al., "Treatment of atrophic vaginitis," *Therapy*, 2007, vol. 4, No. 3, pp. 349-353.  
 Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, *Revista Mexicana de Fisica*, 50, Suplemento 1 pp. 1-3, 2004.  
 Chambin et al., Interest of Multifunctional Lipid Excipients: Case of Gelucire® 44/14, *Drug Development and Industrial Pharmacy*, vol. 31, No. 6, pp. 527-534 (Year: 2005).  
 ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.  
 Cho, Y.A. et al., Transdermal Delivery of Ketorolac Tromethamine: Effects of Vehicles and Penetration Enhancers, *Drug Development and Industrial Pharmacy*, 30(6):557-564, Jun. 2004.  
 Christen et al., Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin, *J Clin Oncol* 11:2417-2426, 1993.



## US 10,206,932 B2

Page 12

(56)

## References Cited

## OTHER PUBLICATIONS

- Christensson et al., Limonene hydroperoxide analogues differ in allergenic activity, *Contact Dermatitis* 2008: 59: 344-352.
- Christensson et al., Limonene hydroperoxide analogues show specific patch test reactions, *Contact Dermatitis*, 70, 291-299, 2014.
- Christensson et al., Positive patch test reactions to oxidized limonene: exposure and relevance, *Contact Dermatitis*, 71, 264-272, 2014.
- Chun et al., Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles . . . , *J. Kor. Pharm. Sci.*, vol. 35, No. 3, pp. 173-177 (2005).
- Cicinelli et al., Direct Transport of Progesterone From Vagina to Uterus, *Obstetrics & Gynecology*, vol. 95, No. 3, March 2000, pp. 403-406.
- Cole, Wayne & Julian, Percy L., *Sterols. I. A Study of the 22-Ketosteroids*, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Committee Opinion, Incidentally Detected Short Cervical Length, Committee of Obstetric Practice, *Obstetrics & Gynecology*, ACOG, vol. 119, No. 4, Apr. 2012, pp. 879-882.
- Comodari, Fernando, Comparison of 17 $\beta$ -estradiol structures from x-ray diffraction and solution NMR, *Magn. Reson. Chem.*, vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A. et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, *The Lancet*, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Corbett et al., "Trends in Pharmacy Compounding for Women's Health in North Carolina: Focus on Vulvodynia," *Southern Medical Journal*, vol. 107, No. 7, Jul. 2014, pp. 433-436.
- Corn Refiners Association, *Corn Oil*, 5th Edition, Washington, D.C., 2006.
- Crandall, Carolyn, "Vaginal Estrogen Preparations: A Review of Safety and Efficacy for Vaginal Atrophy," *Journal of Women's Health*, 2002, vol. 11, No. 10, pp. 857-877.
- CREMER Care, "MIGLYOL® 810, 812 INCI: Caprylic/Capric Triglyceride," CREMER OLEO GmbH & Co. KG, pp. 1-7, available at [http://s3.amazonaws.com/petercremerna/products/spec\\_sheets/159/339/301\\_/originai/MIGL\\_YOL\\_81\\_0\\_812\\_TDS.pdf?1389204445](http://s3.amazonaws.com/petercremerna/products/spec_sheets/159/339/301_/originai/MIGL_YOL_81_0_812_TDS.pdf?1389204445) (Mar. 2013) accessed on Dec. 30, 2016.
- Critchley et al., Estrogen Receptor  $\beta$ , But Not Estrogen Receptor  $\alpha$ , Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium, *The Journal of Clinical Endocrinology & Metabolism*, 2001, vol. 86, No. 3, pp. 1370-1378.
- Dauqan, Egbal M. A., et al., *Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE*, vol. 14, 2011, IACSIT Press, Singapore.
- Dideberg, O. et al., Crystal data on progesterone (C<sub>21</sub>H<sub>30</sub>O<sub>2</sub>), desoxycorticosterone (C<sub>21</sub>H<sub>30</sub>O<sub>3</sub>), corticosterone (C<sub>21</sub>H<sub>30</sub>O<sub>4</sub>) and aldosterone . . . , *J. Appl. Cryst.* vol. 4 pp. 80, 1971.
- Diramio, Jackie A., *Polyethylene Glycol Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs*, Masters of Science Thesis, University of Georgia, Athens, Georgia, 2002, 131 pages.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , *Inter. Journal of Pharmaceutics*, Elsevier, vol. 363, pp. 40-49, 2009.
- Du et al., Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood, *Menopause: The Journal of The North American Menopause Society*, 2013, vol. 20, No. 11, pp. 1-7.
- Duax, William L., et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, *J. Am. Chem. Soc.*, vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R. et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , *J. Thermal Anal.*, vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, *SciFinder, Pharmaceutica Acta Helvetiae*, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Engelhardt et al., Conceptus Influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy, *Biology of Reproduction* 66, 1875-1880 (2002).
- Estradiol, The Merck Index Online, Royal Society of Chemistry, <https://www.rsc.org/Merck-Index/monograph/mono1500003758/estradiol?q=unauthorize>.
- Ettinger et al., Comparison of endometrial growth produced by unopposed conjugated estrogens or by micronized estradiol in postmenopausal women, *Am J Obstet Gynecol* 1997; 176:112-117.
- Excipients for Pharmaceuticals, SASOL OLEFINS & SURFACTANTS GMBH, 2010, 28 pages.
- Faassen, Fried, *Physicochemical Properties and Transport of Steroids across Caco-2 Cells*, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Ferrari, Roseli AP., et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, Piracicaba, Braz.
- Filipsson et al., Concise International Chemical Assessment Document 5: Limonene, first draft, World Health Organization, Geneva, 1998, 36 pages.
- Final Report on the Safety Assessment of BHT, *International Journal of Toxicology*, 21(Suppl. 2):19-94, 2002/.
- Flyvholm, Sensitizing risk of butylated hydroxytoluene B1sed on exposure and effect data, *Contact Dermatitis* 1990: 23: 341-345.
- Fotherby, K., Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy, *Contraception*, 1996; 54:59-69.
- Franklin et al., Characterization of immunoglobulins and cytokines in human cervical mucus: influence of exogenous and endogenous hormones, *Journal of Reproductive Immunology* 42 (1999) 93-106, Elsevier.
- Franz et al., Use of Excised Human Skin to Assess the Bioequivalence of Topical Products, *Skin Pharmacol Physiol* 2009;22:276-286.
- Freedman, R.R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Fuchs et al., The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study, *Cutis. Jun.* 2003;71(6):481-8.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.
- Furness et al., Hormone therapy in postmenopausal women and risk of endometrial hyperplasia (Review), 2012, pp. 1-204, The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
- Gälfvert et al., Free radicals in antigen formation: reduction of contact allergic response to hydroperoxides by epidermal treatment with antioxidants, *British Journal of Dermatology* 2002; 146: 649-656.
- Ganam-Quintanar et al., Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss, *International Journal of Pharmaceutics*, vo. 147, No. 2, Feb. 28, 1997, pp. 165-171 (abstract only).
- Garad S. et al., "Preclinical Development for Suspensions," A.K. Kulshreshtha et al. (eds.), *Pharmaceutical Suspensions: From Formulation Development to Manufacturing*, Springer, New York 2010, pp. 127-176.
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 2012, 8 pages.
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 2012, 6 pages.
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 2012, 5 pages.
- Gattefossé, "Excipients for Safe and Effective Topical Delivery, Drug Development and Delivery" Jul./Aug. 2012, <http://drug-dev.com/Main/B1ck-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#>.

(56)

## References Cited

## OTHER PUBLICATIONS

- Geelen, Math J.H. et al., "Dietary medium-chain fatty acids raise and (n-3) polyunsaturated fatty acids lower hepatic triacylglycerol synthesis in rats," *The Journal of Nutrition*, 1995, 125(10):2449-2456.
- Gillet et al., Induction of amenorrhea during hormone replacement therapy: optimal micronized progesterone dose. A multicenter study, *Maturitas* 19 (1994) 103-115.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, *J. Pharmaceutical & Biomedical Anal.*, vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Giron-Forest, D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, *Thermochimica Acta*, vol. 248 pp. 1-59, 1995, Elsevier.
- Glaser et al, Pilot Study: Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina, *Gynecol Obstet Invest* 2008;66:111-118.
- Golatowski et al., Comparative evaluation of saliva collection methods for proteome analysis, *Clinica Chimica Acta* 419 (2013) 42-46.
- Graham et al, Physiological Action of Progesterone in Target Tissues, *Endocrine Reviews*, 1997, vol. 18, No. 4, pp. 502-519.
- Groothuis et al., Estrogen and the endometrium: lessons learned from gene expression profiling in rodents and human, *Human Reproduction Update*, vol. 13, No. 4 pp. 405-417, 2007.
- Gunstone, Frank D, et al., *Vegetable Oils in Food Technology: Composition, Properties and Uses*, Blackwell Publishing, CRC Press, 2002.
- Gurney, E.P. et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, *J.Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hamid et al., The effects of common solubilizing agents on the intestinal membrane Barrier functions and membrane toxicity in rats, *International Journal of Pharmaceutics* 379 (2009) 100-108, Elsevier.
- Haner, Barbara, Crystal data (I) for some pregnenes and pregnadienes, *Acta Cryst.*, vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Hargrove et al., Menopausal Hormone Replacement Therapy with Continuous Daily Oral Micronized Estradiol and Progesterone, *Obstet Gynecol*, vol. 73, No. 4, Apr. 1989, pp. 606-612.
- Hatton et al., "Safety and efficacy of a lipid emulsion containing medium-chain triglycerides," *Clinical Pharmacy*, 1990, vol. 9, No. 5, pp. 366-371.
- He et al., Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia Induced by Ovariectomy Combined with Estrogen, *Gynecol Obstet Invest* 2013;76:51-56.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, *Pharm Res*, vol. 31 pp. 795-808, 2014, Springer Science.
- Helmy et al., Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats, *Clinic Pharmacol Biopharmaceut*, 2014, S2, 7 pages.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, *Jour. of Mag. Resonance*, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Herman, Aima et al., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," 2014 Royal Pharmaceutical Society, *Journal of Pharmacy and Pharmacology*, pp. 1-13.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Holm et al., "Examination of oral absorption and lymphatic transport of halofantrine in a triple-cannulated canine model after administration in self-microemulsifying drug delivery systems (SMEDDS) containing structured triglycerides," *European Journal of Pharmaceutical Sciences* 20 (2003) 91-97.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, *Mol. Pharmacology*, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hostynek, JJ, Predicting absorption of fragrance chemicals through human skin, *J. Soc. Cosme. Chem.*, 46, 221-229 (Jul./Aug. 1995).
- Hulsmann, Stefan, Stability of Extruded 17 $\beta$ -Estradiol Solid Dispersions, *Pharmaceutical Development and Tech.*, vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Humberstone, Andrew et al., "Lipid-based vehicles for the oral delivery of poorly water soluble drugs," *Advanced Drug Delivery Reviews*, 25 (1997) 103-128.
- Hurn et al., Estrogen as a Neuroprotectant in Stroke, *Journal of Cerebral Blood Flow and Metabolism* 20:631-652, 2000, Lippincott Williams & Wilkins, Inc., Philadelphia.
- Hyder et al., Synthetic Estrogen 17 $\alpha$ -Ethinyl Estradiol Induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17 $\beta$ -Estradiol, *JPET* 290(2):740-747, 1999.
- Idder, Salima, et al., Physicochemical properties of Progesterone, *SciFinder*, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johanson, Gunnar, Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester, *Critical Reviews in Toxicology*, 2000, vol. 30, No. 3, pp. 307-345 (abstract only). <http://informahealthcare.com/doi/abs/a0.1080/10408440091159220>.
- Johnson, William S, et al., Racemic Progesterone, *Tetrahedron Letters* No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Joshi et al., Detection and synthesis of a progestagen-dependent protein in human endometrium, *J Reprod Fert* (1980) 59, 273-285.
- Kanno et al., The OECD Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses: Phase I, *Environmental Health Perspectives* • vol. 109 | No. 8 | Aug. 2001, pp. 785-794.
- Karande, et al. Enhancement of transdermal drug delivery via synergistic action of chemicals, *Biochimica et Biophysica Acta*, 1788:2362-2373, Sep. 2009.
- Karlberg et al., Air oxidation of d-limonene (the citrus solvent) creates potent allergens, *Contact Dermatitis*, 1992: 26: 332-340.
- Karlberg et al., Influence of an anti-oxidant on the formation of allergenic compounds during auto-oxidation of d-limonene, *Ann. Occup. Hyg.*, vol. 38, No. 2, pp. 199-207, 1994.
- Kaunitz, Andrew M., Extended duration use of menopausal hormone therapy, *Menopause: The Journal of the North American Menopause Society*, 2014, vol. 21, No. 6, pp. 1-3.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, *Drug Dev. & Indus. Pharm.*, vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Kharode et al., The Pairing of a Selective Estrogen Receptor Modulator, Bazedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention, *Endocrinology* 149(12):6084-6091, 2008.
- Kim et al., Safety Evaluation and Risk Assessment of d-Limonene, *Journal of Toxicology and Environmental Health, Part B: Critical Reviews*, 2013, 16:1, 17-38 <http://dx.doi.org/10.1080/10937404.2013.769418>.
- Kincl et al., Increasing Oral Bioavailability of Progesterone by Formulation, *Journal of Steroid Biochemistry*, 1978, vol. 9, pp. 83-84.
- Knuth et al., Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations, *Advanced Drug Delivery Reviews*, vol. 11, No. 1-2, Jul.-Aug. 1993, pp. 137-167 (abstract only).
- Koga et al., Enhancing mechanism of Labrasol on intestinal membrane permeability of the hydrophilic drug gentamicin sulfate, *European Journal of Pharmaceutics and Biopharmaceutics* 64 (2006) 82-91.



(56)

## References Cited

## OTHER PUBLICATIONS

- Komm et al., Bazedoxifene Acetate: A Selective Estrogen Receptor Modulator with Improved Selectivity, *Endocrinology* 146(9):3999-4008, 2005.
- Korkmaz, Filiz, Biophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyszminiewski, R. et al., EPR Study of the Stable Radical in a  $\gamma$ -Irradiated Single Crystal of Progesterone, *Jour. of Mag. Resonance*, vol. 46 pp. 300-305, 1982, Academic Press.
- Kubli-Garfias, C. et al., Ab initio calculations of the electronic structure of glucocorticoids, *Jour. of Mol. Structure, Theochem*, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, *Jour. of Mol. Structure, Theochem* vol. 425, pp. 171-179, 1998, Elsevier (abstract only).
- Kuhnert-Brandstaetter and Grimm. Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen.II, *Mikrochimica Acta*, vol. 1, pp. 127-139, 1968.
- Kuhnert-Brandstaetter and Junger and Kofler. Thermo-microscopic and spectrophotometric: Determination of steroid hormones, *Microchemical Journal* 9, pp. 105-133, 1965.
- Kuhnert-Brandstaetter and Kofler. Zur mikroskopischen Identitätsprüfung und zur Polymorphie der Sexualhormone, *Mikrochimica Acta*, vol. 6, pp. 847-853, 1959.
- Kuhnert-Brandstaetter and Linder. Zur Hydratbildung bei Steroidhormonen, *Sci. Pharm*, vol. 41(2), pp. 109-116, 1973.
- Kumasaka et al., Effects of Various Forms of Progestin on the the Estrogen-Primed, Ovariectomized Rat, *Endocrine Journal* 1994, 41(2), 161-169.
- Kuon et al., A Novel Optical Method to Assess Cervical Changes during Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor, *Am J Obstet Gynecol*. Jul. 2011 ; 205(1): 82.e15-82.e20.
- Kuon et al., Actions of progestins for the inhibition of cervical ripening and uterine contractions to prevent preterm birth, *FVV in OBGYN*, 2012, 4 (2): 110-119.
- Kuon et al., Pharmacological actions of progestins to inhibit cervical ripening and prevent delivery depend upon their properties, the route of administration and the vehicle, *Am J Obstet Gynecol*. May 2010 ; 202(5): 455.e1-455.e9.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, *Journal of Steroid Biochemistry & Molecular Biology*, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , *Drug Development and Industrial Pharmacy, Informa Healthcare* vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , *Jour. of Pharm. Sci.*, vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steroids, *Pharmaceutical Research*, vol. 22(5) May 2005, Springer Science+Business Media.
- Lane, Majella E., "Skin penetration enhancers," *International Journal of Pharmaceutics* 447 (2013) 12-21.
- Lauer et al., "Evaluation of the hairless rat as a model for in vivo percutaneous absorption," *Journal of Pharmaceutical Sciences*, vol. 86, No. 1, Jan. 1997, pp. 13-18.
- Leonetti et al., Transdermal progesterone cream as an alternative progestin in hormone therapy, *Alternative Therapies*, Nov./Dec. 2005, vol. 11, No. 6, pp. 36-38.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, *Fertility and Sterility*, vol. 79(1), Jan. 2003.
- Lewis, John G. et al., Caution on the use of saliva measurements to monitor absorption of progesterone from transdermal creams in postmenopausal women, *Maturitas*, *The European Menopause Journal*, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroidal conformation of 17 $\alpha$ - and 17 $\beta$ -estradiol in the absence and presence of lipi . . . , *Steroids*, Elsevier, vol. 77, pp. 185-192, 2012.
- Lindmark, Tuulikki et al., "Absorption Enhancement through Intracellular Regulation of Tight Junction Permeability by Medium Chain Fatty Acids in Caco-2 Cells," *JPET* 284(1):362-369, 1998.
- Lindmark, Tuulikki et al., "Mechanisms of Absorption Enhancement by Medium Chain Fatty Acids in Intestinal Epithelial Caco-2 Cell Monolayers," *JPET* 275(2):958-964, 1995.
- Lobo, R.A., Foreword, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Lopes, Luciana B. et al., Enhancement of transdermal delivery of progesterone using medium-chain mono and diglycerides as skin penetration enhancers, *Pharmaceutical Development and Technology*, 14:5, 524-529, Mar. 2009.
- López-Belmonte, Corrigendum to "Comparative uterine effects on ovariectomized rats after repeated treatment with different vaginal estrogen formulations" [*Maturitas* 72 (2012) 353-358], *Maturitas* 74 (2013) 393, Elsevier.
- Lucy et al., Gonadotropin-releasing hormone at estrus: lutenizing hormone, estradiol, and progesterone during . . . *Biol Reprod Sep.* 1986;35(2):300-311 (abstract only).
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, *J Thermal Anal.*, vol. 40 pp. 405-411, 1993, Wiley.
- Mac Bride, Maire B. et al., "Vulvovaginal Atrophy," *Mayo Clin Proc*, Jan. 2010, 85(1):87-94.
- Madishetti et al., Development of domperidone bilayered matrix type transdermal patches: physicochemical, in vitro and ex vivo characterization, *DARU* vol. 18, No. 3, 2010, pp. 221-229.
- Magness, R.R., et al., Estrone, Estradiol-17 $\beta$  and Progesterone Concentrations in Uterine Lymph and Systematic Blood throughout the Porcine Estrone Estrous Cycle, *Journal of Animal Science*, vol. 57, pp. 449-455, ISU, 1983.
- Manson, JoAnn E. et al., "Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials," *JAMA*, Oct. 2, 2013, vol. 310, No. 13, pp. 1353-1368.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, *Catalent Pharma Solutions*, Somerset, NJ, Mar. 2011.
- Mesley, R.J., Clathrate Formation from Steroids, *Chemistry and Industry*, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wenbin, et al., Chemical Properties of Progesterone, *SciFinder*, 2014, American Chemical Society & US Natl. Lib. of Med.
- Miles et al., Pharmacokinetics and endometrial tissue levels of progesterone after administration by Intramuscular and vaginal routes: a comparative study, *Fertility and Sterility*, vol. 62, No. 3, Sep. 1994, pp. 485-490.
- Miller et al., Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast, *Journal of Cancer Therapy*, 2012, 3, 749-754.
- Monti, D. et al., Effect of different terpene-containing essential oils on permeation of estradiol through hairless mouse skin, *International Journal of Pharmaceutics*, 237:209-24, 2002.
- Mueck, A.O. et al., Genomic and non-genomic actions of progestogens in the breast, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between  $\alpha$ - and  $\beta$ - Forms of Crystalline Progesterone, *J. Pharmaceutical Sciences*, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Ng, Jo-Han et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , *Drug Devel. & Indust. Pharmacy*, 35(9) pp. 1035, 2009.

## US 10,206,932 B2

Page 15

(56)

## References Cited

## OTHER PUBLICATIONS

- Nilsson et al., Analysis of Contact Allergenic Compounds in Oxidized d-Limonene, *Chromatographia* vol. 42, No. 3/4, Feb. 1996, pp. 199-205.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- NuGen, What is NuGen HP Hair Growth System.
- NuGest900, NuGest 900™.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical application of pregersterone cream to pre-and post-menopausal women, *Clinical Endocrinology*, vol. 53 pp. 615-620, Blackwell Science 2000.
- Opinion on the Diethylene Glycol Monoethyl Ether (DEGEE), Scientific Committee on Consumer Products, Dec. 19, 2006, 27 pages.
- Otterson, K., The Drug Quality and Security Act—Mind the Gaps, *n engl j med* 370;2 nejm.org Jan. 9, 2014, pp. 97-99.
- Palamakula et al., Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components, *Pharmaceutical Technology* Oct. 2004, pp. 74-88.
- Panay et al., The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy, *Menopause International: The Integrated Journal of Postreproductive Health*, published online May 23, 2013, Sage Publications. <http://min.sagepub.com/content/early/2013/05/23/1754045313489645.1>.
- Panchangnula et al., Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol . . . , *J Pharm Pharmacol*. Sep. 1991;43(9):609-614 (abstract only).
- Parasuraman et al., Blood sample collection in small laboratory animals, *Journal of Pharmacology & Pharmacotherapeutics* | Jul.-Dec. 2010 | vol. 1 | Issue 2, pp. 87-93.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, *Arch Pharm Res*, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3,17b-diol solvate: estradiol-methanol-water, *Crystal Structure Comm.*, *Int'l Union of Crystallography*, ISSN 0108-2701, 2003.
- Patel et al., Transdermal Drug Delivery System: A Review, [www.thepharmajournal.com](http://www.thepharmajournal.com), vol. 1, No. 4, 2012, pp. 78-87.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, *Intl. Jour. of Pharma.*, vol. 177 pp. 231-245, 1999, Elsevier.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, *SciFinder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pfaus et al., Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist, *PNAS*, Jul. 6, 2004, vol. 101, No. 27, pp. 10201-10204.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pickles, VR, Cutaneous reactions to injection of progesterone solutions into the skin, *Br Med Journal*, Aug. 16, 1952, pp. 373-374.
- Pinkerton et al., What are the concerns about custom-compounded "bioidentical" hormone therapy? *Menopause: The Journal of the North American Menopause Society*, vol. 21, No. 12, 2014, pp. 1-3.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, *J. Steroid Biochem. Mol. Biol.* (2014), Elsevier.
- Pisegna, Gisela L., A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.
- Portman, David et al., One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy, *Menopause*, vol. 22, No. 11, 2015, pp. 000/000 (8 pages).
- Position Statement, Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society (NAMS), *Menopause*, vol. 20, No. 9, pp. 888-902.
- Potluri, Praveen and Guru V. Betageri, "Mixed-micellar proliposomal systems for enhanced oral delivery of progesterone," *Drug Delivery*, 2006, vol. 13, No. 3, pp. 227-232.
- Practice Bulletin No. 141, Management of Menopausal Symptoms, *Obstetrics & Gynecology*, ACOG, vol. 123, No. 1, Jan. 2014, pp. 202-216.
- Prajapati Hetal N. et al., "A Comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water Phase Diagram, Solubility Determination and Dispersion Testing for Application in Pharmaceutical Dosage Form Development," *Pharm Res.* Jan. 2012; 29(1): 285-305. Published online Aug. 23, 2011. doi: 10.1007/s11095-011-0541-3.
- Prajapati Hetal N. et al., "Effect of Difference in Fatty Acid Chain Lengths of Medium-Chain Lipids on Lipid/Surfactant/Water Phase Diagrams and Drug Solubility," *J. Excipients and Food Chem.* 2 (3) 2011:73-88.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/Surfactant/Water, [Springerlink.com](http://Springerlink.com), pp. 1-21, Apr. 2011.
- Prausnitz et al., Transdermal drug delivery, *Nat Biotechnol.* Nov. 2008 ; 26(11): 1261-1268.
- Price, Sarah L, The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Product Information Sheet, Body Bllance Cream, Tahitian Noni International, 2013, 1 page.
- Product Safety Assessment: Diethylene Glycol Monoethyl Ether, Created: Sep. 24, 2007 The Dow Chemical Company Page, 5 pages.
- Progesterone, The Merck Index Online, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Prodynova TS 100, available online at file:///C:/Users/Call%20Family/Desktop/Prodynova%20TS%20100%2012%20Patches\_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Provider Data Sheet, About Dried Blood Spot Testing, ZRT Laboratory, 2014, 3 pages.
- Rahn et al., Vaginal Estrogen for Genitourinary Syndrome of Menopause a Systematic Review, *Obstet Gynecol* 2014;124(6):1147-56.
- Rao, Rajeswara et al., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *J Bioequiv Availab.* 2014, 6: 139-143.
- Rao, R. et al., "The Affect of Capmul, Labrafil and Transcutol on Progesterone 100 Mg Soft Capsules Bioavailability in Indian Healthy Adult Postmenopausal Female Subjects Under Fasting Conditions," *Bioequivalence & Bioavailability*, 7(2):095-107, 2015.
- Reisman et al., Topical Application of the Synthetic Triterpenoid RTA 408 Protects Mice from Radiation-Induced Dermatitis, *Radiation Research* 181, 512-520 (2014).
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly(D,L-lactide-co-glycolide) Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Ross et al., Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women, *AnnJ Obstet Gynecol*, Oct. 1997, vol. 177, No. 4, pp. 937-941.
- Ruan et al., Systemic progesterone therapy—Oral, vaginal, injections and even transdermal? *Maturitas* 79 (2014) 248-255, Elsevier.
- Salem, HF, Sustained-release progesterone nanosuspension following intramuscular injection in ovariectomized rats, *International Journal of Nanomedicine* 2010:5 943-954, Dove Press.
- Sallee, Verney L. et al., "Determinants of intestinal mucosal uptake of short- and medium-chain fatty acids and alcohols," *Journal of Lipid Research*, 1973, vol. 14, 475-484.

## US 10,206,932 B2

Page 16

(56)

## References Cited

## OTHER PUBLICATIONS

- Salole, Eugene G., Estradiol, Analytical Profiles of Drug Substances, vol. 15, pp. 283-318, 1986.
- Salole, Eugene G., The physicochemical properties of oestradiol, Journal of Pharmaceutical & Biomedical Analysis, vol. 5, No. 7, pp. 635-648, 1987.
- Santen, R.J., Menopausal hormone therapy and breast cancer, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Santen, R.J., Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels, CLIMACTERIC 2014;17:1-14.
- Sarkar, BISU, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream™ and HRT Cream™ B1se . . . , J Steroids Horm Sci, 4:2, 2013.
- Sarpal, K. et al., "Self emulsifying drug delivery systems: a strategy to improve oral bioavailability," Current Research & Information on Pharmaceuticals Sciences (CRIPS), 2010, vol. 11, No. 3, pp. 42-49.
- Sarrel, et al., The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years, American Journal of Public Health, Research and Practice, e1-e6. Published online ahead of print Jul. 18, 2013.
- Satyanarayana, D. et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, Asian J. Chem., vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, SciFinder, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A.E., The "newer" progestogens and postmenopausal hormone therapy (HRT), J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Schindler, Aldof E. et al., Classification and pharmacology of progestins, Maturitas 46S1 (2003) S7-S16.
- Schutte et al., A tissue engineered human endometrial stroma that responds to cues for secretory differentiation, decidualization and menstruation, Fertil Steril. Apr. 2012 ; 97(4): 997-1003, Elsevier.
- Schweikart et al., Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats, Toxicologic Pathology, 42: 1188-1196, 2014.
- SciFinder Scholar Prednisone Chemical Properties, SciFinder, 2014, pp. 1-7, National Library of Medicine.
- SciFinder Scholar Prednisone Physical Properties, SciFinder, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, SciFinder, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Search Report, Extended European Search Report for EP13741053. 6, dated Jul. 1, 2015.
- Search Report, Extended European Search Report for EP13807188. 1, dated Nov. 23, 2015.
- Search Report, International Search Report and Written Opinion for PCT/US12/66406, dated Jan. 24, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/23309, dated Apr. 9, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46442, dated Nov. 1, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46443, dated Oct. 31, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46444, dated Oct. 31, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US13/46445, dated Nov. 1, 2013.
- Search Report, International Search Report and Written Opinion for PCT/US14/61811, dated Jan. 21, 2015.
- Search Report, International Search Report and Written Opinion for PCT/US15/23041, dated Jun. 30, 2015.
- Search Report, International Search Report and Written Opinion for PCT/US15/42621, dated Oct. 29, 2015.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), Crystal Structure Comm., vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Shao et al., Review Open Access Direct effects of metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma, Journal of Experimental & Clinical Cancer Research 2014, 33(1):41, 11 pages.
- Sharma, H.C., et al., Physical Properties of Progesterone Selected Refer, SciFinder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Shrier et al., "Mucosal Immunity of the Adolescent Female Genital Tract," Journal of Adolescent Health, 2003; 32:183-186.
- Shufelt et al., Hormone therapy dose, formulation, route delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study, Menopause: The Journal of the North American Menopause Society, vol. 21, No. 3, 2014, pp. 1-7, 2013.
- Siew, Adeline, moderator, Bioavailability Enhancement with Lipid-Based Drug-Delivery Systems, Pharmaceutical Technology, Aug. 2014, pp. 28, 30-31.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>.
- Simon et al., Effective Treatment of Vaginal atrophy with an Ultra-low-dose estradiol vaginal tablet, Obstetrics & Gynecology, vol. 112, No. 5, Nov. 2008, pp. 1053-1060.
- Simon, James A., What if the Women's Health Initiative had used transdermal estradiol and oral progesterone instead? Menopause: The Journal of the North American Menopause Society, 2014, vol. 21, No. 7, pp. 1-15.
- Sitruk-Ware et al., Progestogens in hormonal replacement therapy: new molecules, risks, and benefits, Menopause: The Journal of the North American Menopause Society. vol. 9, No. 1, pp. 6-15, 2002.
- Sitruk-Ware, Regine, "Pharmacological profile of progestins," Maturitas 47 (2004) 277-283.
- Sitruk-Ware, Regine, Oral Micronized Progesterone—Bioavailability pharmacokinetics, pharmacological and therapeutic implications—A review, Contraception, Oct. 1987, vol. 36, No. 4, pp. 373-402.
- Smith et al., Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens, JAMA Internal Medicine, Published online Sep. 30, 2013, E1-E7. [jamainternalmedicine.com](http://jamainternalmedicine.com).
- Smyth et al., Summary of Toxicological Data, A 2-yr Study of Diethylene Glycol Monoethyl Ether in Rats, Fd Cosmet. Toxicol. vol. 2, pp. 641-642, 1964.
- Stanczyk et al., Thereapeutically equivalent pharmacokinetic profile across three application sites for AG200-15, a novel low-estrogen dose contraceptive patch, Contraception, 87 (2013) pp. 744-749.
- Stanczyk, F.Z. et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," Menopause: The Journal of the North American Menopause Society, 2005, vol. 12, No. 2, pp. 232-237.
- Stanczyk, F.Z. et al., Ethinyl estradiol and 17 $\beta$ -estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment, Contraception 87 (Jun. 2013) vol. 87, No. 6, pp. 706-727.
- Stanczyk, F.Z., "All progestins are not created equal," Steroids 68 (2003) 879-880.
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective?" Climacteric 2014;17 (Suppl 2):8-11.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Stein, Emily A. et al., Progesterone Physical Properties, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stephenson et al., "Transdermal progesterone: Effects on Menopausal symptoms and on thrombotic, anticoagulant, and inflammatory factors in postmenopausal women," Int J Pharmaceutical Compounding, vol. 12, No. 4, Jul./Aug. 2008, pp. 295-304.
- Strickley, Robert T., Solubilizing excipients in oral and injectable formulations, Pharmaceutical Research Feb. 2004, vol. 21, Issue 2, pp. 201-230 (abstract only).
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, Journal of Food Science, vol. 47, pp. 36-39, 1981.

## US 10,206,932 B2

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(56)

## References Cited

## OTHER PUBLICATIONS

Struhar, M. et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.

Sullivan et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," Food and Chemical Toxicology, 72 (2014) pp. 40-50.

Sun, Jidong, D-Limonene: Safety and Clinical Applications, Alternative Medicine Review vol. 12, No. 3, 2007, pp. 259-264.

Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.

Takacs M. et al., The light sensitivity of corticosteroids in crystalline form, Pharmaceutica acta Helvetica, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.

Tan, Melvin S. et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.

Tang et al., Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat, Biology of Reproduction 31, 399-413 (1984).

Tas et al., Comparison of antiproliferative effects of metformine and progesterone on estrogen-induced endometrial hyperplasia in rats, Gynecol Endocrinol, Early Online: 1-4, 2013. <http://informahealthcare.com/gye>.

Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.

Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , Intl. J. of Pharmaceut., vol. 339 pp. 157-167, 2007, Elsevier.

Thomas, Peter, Characteristics of membrane progesterin receptor alpha (mPR $\alpha$ ) and progesterone membrane receptor component 1 (PGMRC1) and their roles in mediating rapid progestin actions, Frontiers in Neuroendocrinology 29 (2008) 292-312.

Tripathi, R. et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, AAPS PharmSciTech, vol. 11, No. 3, Sep. 2010.

Trommer et al., Overcoming the stratum Corneum: The modulation of Skin Penetration, Skin Pharmacol Physiol 2006;19:106-121.

Tuleu et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying Formulation of Progesterone Presented in a Pellet and Liquid Form Compared with an Aqueous Suspension of Progesterone," Journal of Pharmaceutical Sciences, vol. 93, No. 6, Jun. 2004, pp. 1495-1502.

Ueda et al., Topical and Transdermal Drug Products, Pharmacopeial Forum, vol. 35(3) [May-Jun. 2009], 750-754.

USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.

USP, Certificate-Corn Oil, Lot G0L404, Jul. 2013.

USP, Lauroyl Polyoxylglycerides, Safety Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.

USP, Monographs: Progesterone, USP29, [www.pharmacopeia.cn/v29240/usp29nf24s0\\_m69870.html](http://www.pharmacopeia.cn/v29240/usp29nf24s0_m69870.html), search done: Feb. 25, 2014.

USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.

USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.

USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.

USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.

U.S. Appl. No. 13/843,428, filed Jul. 2, 2015 Non-Final Office Action.

U.S. Appl. No. 14/106,655, filed Jun. 19, 2015 Final Office Action.

U.S. Appl. No. 13/684,002, filed Mar. 20, 2013 Non-Final Office Action.

U.S. Appl. No. 13/684,002, filed Jul. 16, 2013 Final Office Action.

U.S. Appl. No. 13/684,002, filed Dec. 6, 2013 Notice of Allowance.

U.S. Appl. No. 13/843,362, filed Mar. 16, 2015 Restriction Requirement.

U.S. Appl. No. 13/843,428, filed Apr. 14, 2015 Restriction Requirement.

U.S. Appl. No. 14/099,545, filed Feb. 18, 2014 Non-Final Office Action.

U.S. Appl. No. 14/099,545, filed Jul. 14, 2014 Notice of Allowance.

U.S. Appl. No. 14/099,562, filed Feb. 20, 2014 Restriction Requirement.

U.S. Appl. No. 14/099,562, filed Mar. 27, 2014 Non-Final Office Action.

U.S. Appl. No. 14/099,562, filed Jul. 2, 2014 Final Office Action.

U.S. Appl. No. 14/099,562, filed Dec. 10, 2014 Notice of Allowance.

U.S. Appl. No. 14/099,571, filed Mar. 28, 2014 Restriction Requirement.

U.S. Appl. No. 14/099,571, filed Jul. 15, 2014 Notice of Allowance.

U.S. Appl. No. 14/099,582, filed Apr. 29, 2014 Restriction Requirement.

U.S. Appl. No. 14/099,582, filed Jun. 17, 2014 Non-Final Office Action.

U.S. Appl. No. 14/099,582, filed Nov. 7, 2014 Notice of Allowance.

U.S. Appl. No. 14/099,582, filed Jan. 22, 2015 Notice of Allowance.

U.S. Appl. No. 14/099,598, filed May 13, 2014 Restriction Requirement.

U.S. Appl. No. 14/099,598, filed Jul. 3, 2014 Non-Final Office Action.

U.S. Appl. No. 14/099,598, filed Dec. 10, 2014 Notice of Allowance.

U.S. Appl. No. 14/099,612, filed Mar. 20, 2014 Restriction Requirement.

U.S. Appl. No. 14/099,612, filed Oct. 30, 2014 Non-Final Office Action.

U.S. Appl. No. 14/099,612, filed Nov. 26, 2014 Notice of Allowance.

U.S. Appl. No. 14/099,623, filed Mar. 5, 2014 Restriction Requirement.

U.S. Appl. No. 14/099,623, filed Jul. 18, 2014 Non-Final Office Action.

U.S. Appl. No. 14/099,623, filed Dec. 15, 2014 Notice of Allowance.

U.S. Appl. No. 14/106,655, filed Jul. 3, 2014 Restriction Requirement.

U.S. Appl. No. 14/106,655, filed Dec. 8, 2014 Non-Final Office Action.

U.S. Appl. No. 14/125,554, filed Dec. 5, 2014 Restriction Requirement.

U.S. Appl. No. 14/125,554, filed Apr. 14, 2015 Non-Final Office Action.

U.S. Appl. No. 14/136,048, filed Nov. 4, 2014 Restriction Requirement.

U.S. Appl. No. 14/136,048, filed Mar. 12, 2015 Non-Final Office Action.

U.S. Appl. No. 14/475,814, filed Oct. 1, 2014 Non-Final Office Action.

U.S. Appl. No. 14/475,814, filed Feb. 13, 2015 Notice of Allowance.

U.S. Appl. No. 14/475,864, filed Oct. 2, 2014 Non-Final Office Action.

U.S. Appl. No. 14/475,864, filed Feb. 11, 2015 Notice of Allowance.

U.S. Appl. No. 14/476,040, filed Mar. 26, 2015 Restriction Requirement.

U.S. Appl. No. 14/521,230, filed Dec. 5, 2014 Restriction Requirement.

U.S. Appl. No. 14/521,230, filed Feb. 18, 2015 Non-Final Office Action.

U.S. Appl. No. 14/624,051, filed Apr. 7, 2015 Non-Final Office Action.



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(56)

## References Cited

## OTHER PUBLICATIONS

- Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens, *Fertility and Sterility*, vol. 75(6) pp. 1065, Jun. 2001.
- Voegtline et al., Dispatches from the interface of salivary bioscience and neonatal research, *Frontiers in Endocrinology*, Mar. 2014, vol. 5, article 25, 8 pages.
- Waddell et al., Distribution and metabolism of topically applied progesterone in a rat model, *Journal of Steroid Biochemistry & Molecular Biology* 80 (2002) 449-455.
- Waddell et al., The Metabolic Clearance of Progesterone in the Pregnant Rat: Absence of a Physiological Role For the Lung, *Biology of Reproduction* 40, 1188-1193 (1989).
- Walter et al., The role of progesterone in endometrial angiogenesis in pregnant and ovariectomised mice, *Reproduction* (2005) 129 765-777.
- Weber, E.J., Corn Lipids, *Cereal Chem.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Weintraub, Arlene, "Women fooled by untested hormones from compounding pharmacies," *Forbes*, Feb. 20, 2015; retrieved online at <http://onforb.es/1LIUm1V>, on Feb. 23, 2015, 3 pages.
- Whitehead et al., Absorption and metabolism of oral progesterone, *The British Medical Journal*, vol. 280, No. 6217 (Mar. 22, 1980), pp. 825-827, BMJ Publishing Group.
- Wiranidchamong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, *Thermochimica Acta* 485, Elsevier, pp. 57, 2009.
- Wood et al., Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys, *Breast Cancer Res Treat* (2007) 101:125-134.
- Wren et al., Effect of sequential transdermal progesterone cream on endometrium, bleeding pattern, and plasma progesterone and salivary progesterone levels in postmenopausal women, *Climacteric*, 2000, 3(3), pp. 155-160. <http://dx.doi.org/10.1080/13697130008500109>.
- Wu et al., Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus, *Biology of Reproduction* 69, 1308-1317 (2003).
- Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning I: Solubility of Nonelectrolytes in Water, *J. of Pharmaceutical Sciences*, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, *Handbook of Aqueous Solubility Data, Solutions*, 2003, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
- Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, *Journal of Steroid Biochem & Mol Biology*, vol. 86 pp. 477-486, 2003.
- Zava, David T. et al., Percutaneous absorption of progesterone, *Maturitas* 77 (2014) 91-92, Elsevier.
- Zava, David T., *Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues*, Script, ZRT Laboratory, pp. 4-5. [http://www.zrtlab.com/component/docman/cat\\_view/10-publications?Itemid](http://www.zrtlab.com/component/docman/cat_view/10-publications?Itemid).

\* cited by examiner

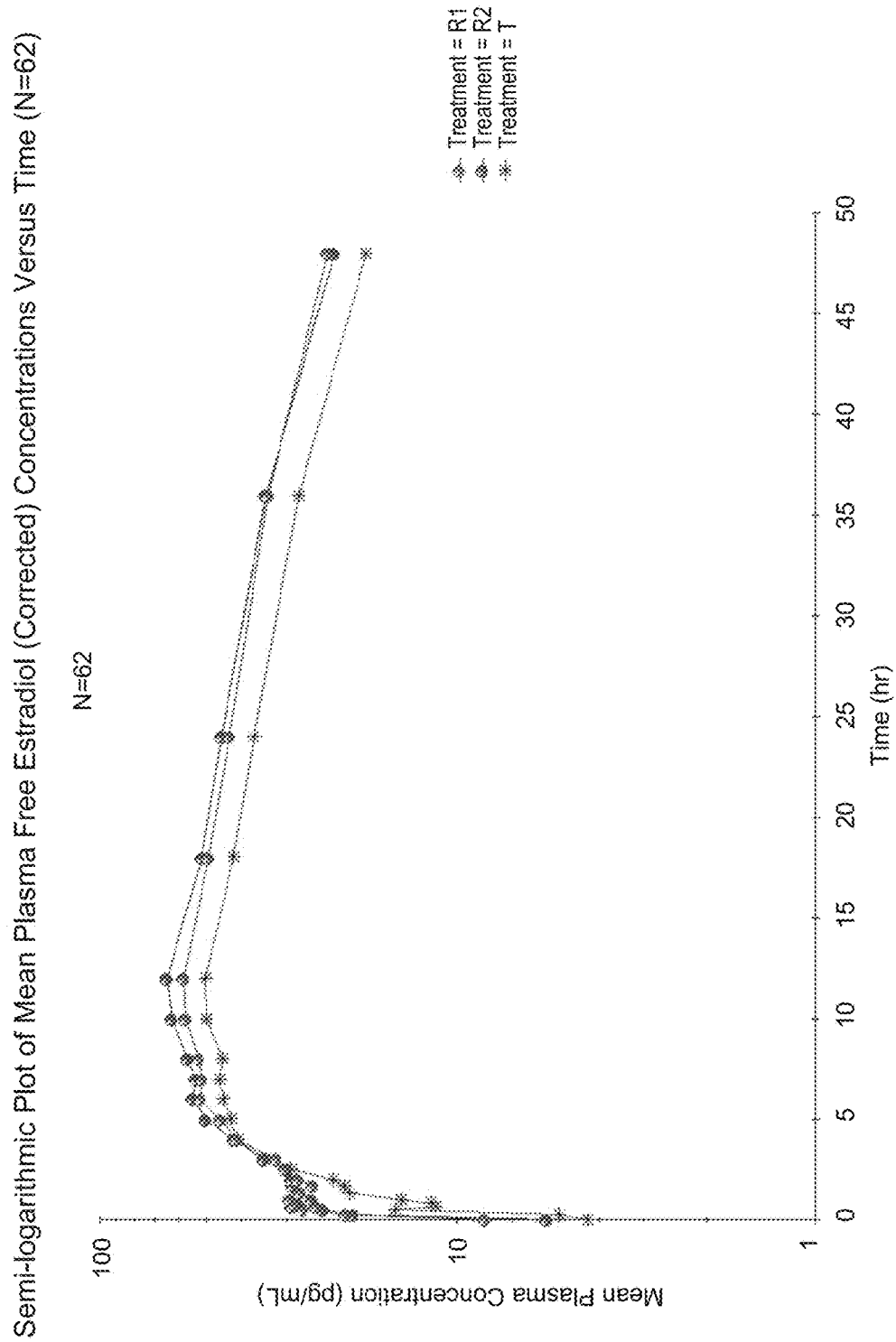


FIG. 1



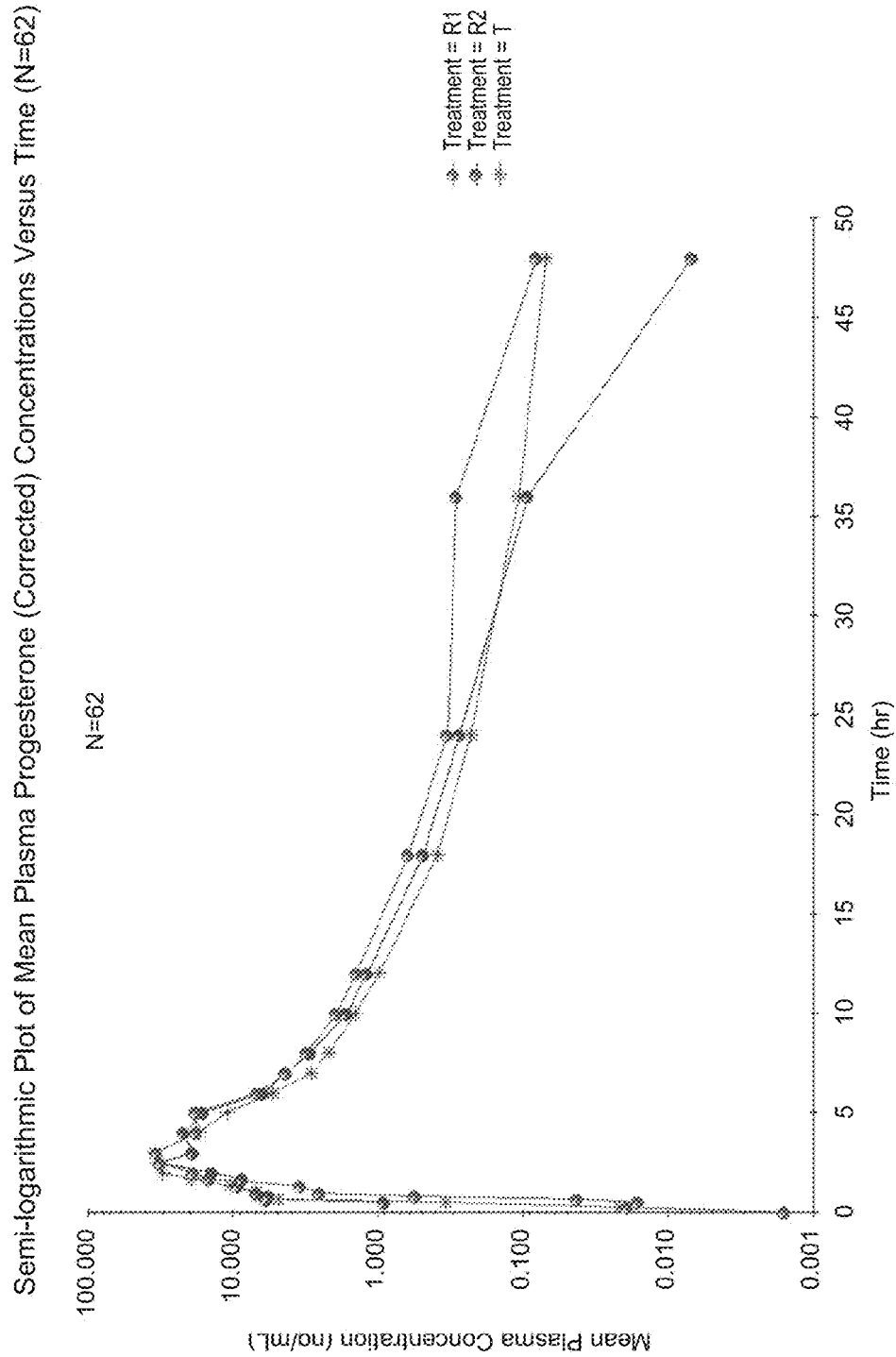


FIG. 2

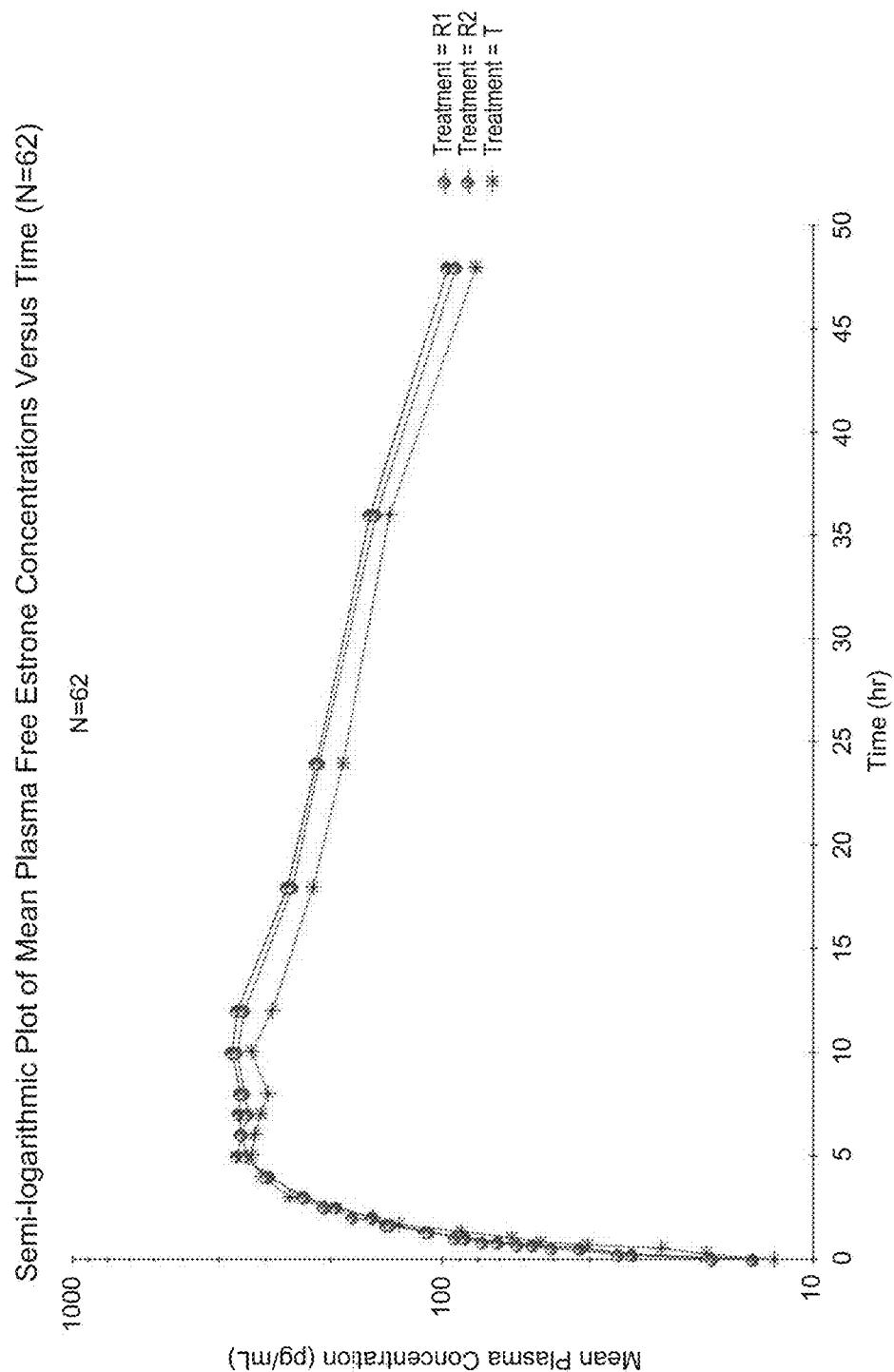


FIG. 3

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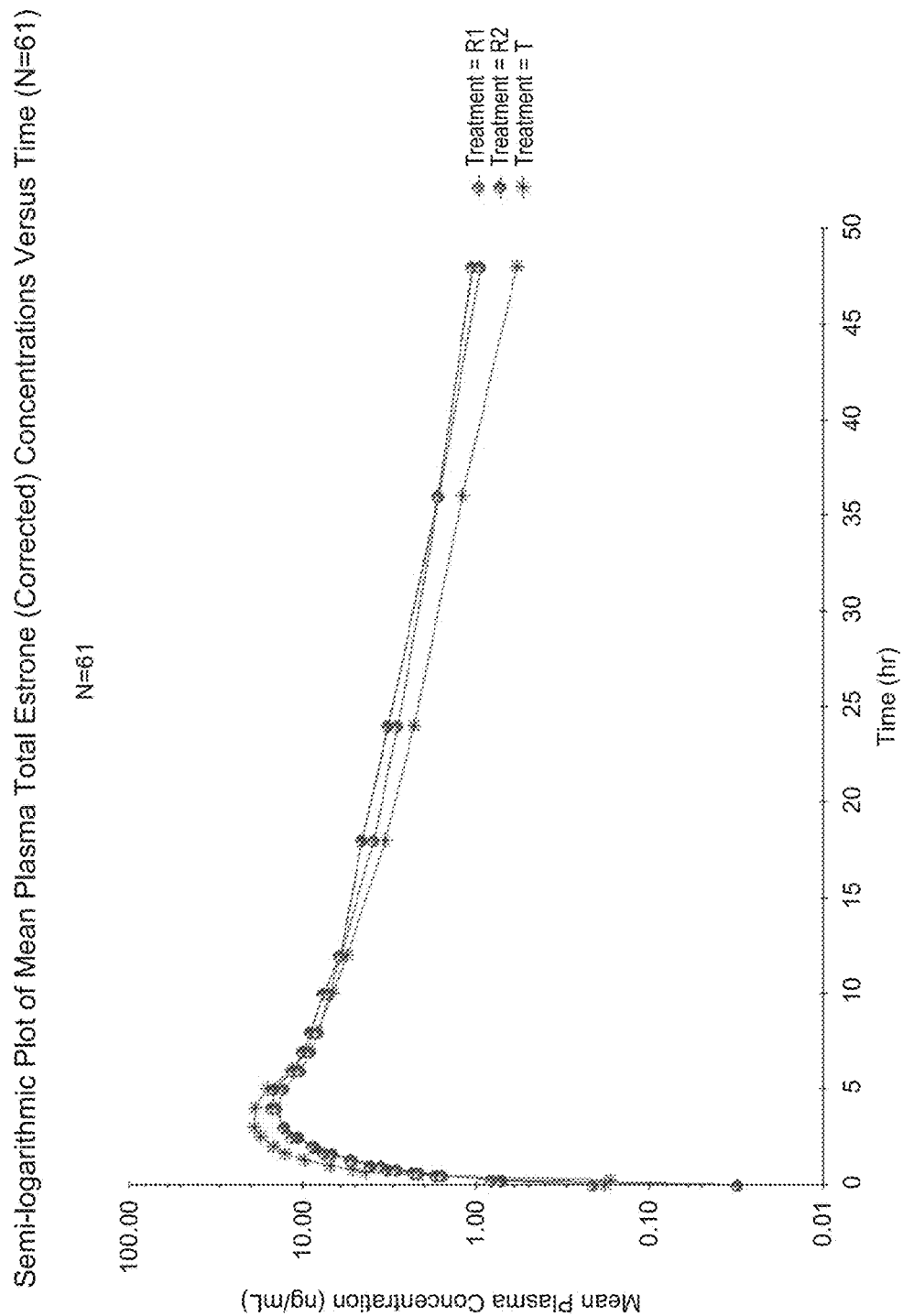


FIG. 4

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# NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Ser. No. 62/002,090, filed May 22, 2014, the content of which is incorporated by reference herein in its entirety.

## FIELD OF THE INVENTION

This application relates to pharmaceutical compositions and methods for hormone replacement therapy.

## BACKGROUND OF THE INVENTION

Hormone Replacement Therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones in a pre-menopausal, peri-menopausal, menopausal or post-menopausal subject.

## BRIEF SUMMARY OF THE INVENTION

In one aspect, pharmaceutical compositions for co-administering estradiol and progesterone to a subject in need of natural hormone replacement therapies are provided. In some embodiments, the pharmaceutical composition comprises: solubilized estradiol, suspended progesterone, and a solubilizing agent, wherein the solubilizing agent is a medium chain (C6-C12) oil and wherein the pharmaceutical composition, when administered to a subject, produces in a plasma sample from the subject one or more pharmacokinetic parameters as described herein (e.g., an area under the curve ( $AUC_{(0-t)}$ ) or a  $C_{max}$  for estradiol, progesterone, estrone, or total estrone as described herein, e.g., in Tables 18-21).

In some embodiments, the pharmaceutical composition comprises a solubilizing agent that comprises a glyceride of at least one C6-C12 fatty acid. In some embodiments, the glyceride ester is a mixture of mono- and diglycerides (e.g., glyceryl caprylate/caprate). In some embodiments, the fatty acid is predominantly a C8 to C10 fatty acid. In some embodiments, the pharmaceutical composition further comprises a surfactant (e.g., lauroyl polyoxyglyceride). In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprises progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.25 mg and comprises progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.50 mg and comprises progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 0.50 mg and comprises progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises estradiol at a dosage of about 1 mg and comprises progesterone at a dosage of about 100 mg. In some embodi-

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ments, the pharmaceutical composition comprises estradiol at a dosage of about 2 mg and comprises progesterone at a dosage of about 200 mg.

In some embodiments, the pharmaceutical composition comprises about 0.25 mg estradiol and about 50 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ( $AUC_{(0-t)}$ ) for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an  $AUC_{(0-t)}$  for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; and a  $C_{max}$  for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml.

In some embodiments, administration of the composition to subject further produces, in a plasma sample from the subject, one or both parameters selected from: an  $AUC_{(0-t)}$  for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; and a  $C_{max}$  for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.25 mg estradiol and about 50 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an  $AUC_{(0-t)}$  for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml and (b) a  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; and
- (ii) one or both of (a) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an  $AUC_{(0-t)}$  for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml and (b) a  $C_{max}$  for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; and optionally
- (iv) one or both of (a) an  $AUC_{(0-t)}$  for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml and (b) a  $C_{max}$  for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 0.50 mg estradiol and about 50 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an  $AUC_{(0-t)}$

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for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, and a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, and a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.50 mg estradiol and about 50 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an  $UC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 0.50 mg estradiol and about 100 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ( $AUC_{(0-t)}$ ) for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, and a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, and a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.50 mg estradiol and about 100 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a

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$C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally

- (iii) one or both of (a) an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, a pharmaceutical composition for co-administering estradiol and progesterone to a human subject in need thereof comprises about 1 mg estradiol and about 100 mg progesterone, and administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ( $AUC_{(0-t)}$ ) for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an  $AUC_{(0-t)}$  for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml, and a  $C_{max}$  for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from: an  $AUC_{(0-t)}$  for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml, and a  $C_{max}$  for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In some embodiments, the pharmaceutical composition comprises about 0.50 mg estradiol and about 100 mg progesterone, and administration of the composition to a subject produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an  $AUC_{(0-t)}$  for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml and (b) a  $C_{max}$  for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; and
- (ii) one or both of (a) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally
- (iii) one or both of (a) an  $AUC_{(0-t)}$  for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml and (b) a  $C_{max}$  for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; and optionally
- (iv) one or both of (a) an  $AUC_{(0-t)}$  for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml and (b) a  $C_{max}$  for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In some embodiments, the pharmaceutical composition has the blood plasma estradiol concentration profile of FIG. 1. In some embodiments, the pharmaceutical composition has the blood plasma progesterone concentration profile of FIG. 2. In some embodiments, the pharmaceutical composition has the blood plasma estrone concentration profile of FIG. 3. In some embodiments, the pharmaceutical composition has the blood plasma total estrone concentration profile of FIG. 4.

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In some embodiments, the one or more parameters as described herein (e.g., the  $AUC_{(0-t)}$  or  $C_{max}$  for progesterone, estradiol, estrone, or total estrone) are measured at regular intervals (e.g., about every 30 minutes, about every 60 minutes, or about every 90 minutes) or at irregular intervals over a period of time such as 24 hours or 48 hours. In some embodiments, the one or more parameters as described herein (e.g., the  $AUC_{(0-t)}$  or  $C_{max}$  for progesterone, estradiol, estrone, or total estrone) are measured at about 0.25 hr, 0.5 hr, 0.67 hr, 0.83 hr, 1 hr, 1.33 hr, 1.67 hr, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr, 10 hr, 12 hr, 18 hr, 24 hr, 36 hr, or 48 hr after administering the pharmaceutical composition to the subject. In some embodiments, the one or more parameters as described herein are measured at regular or irregular intervals following the administration of a single dose or of a first dose of the pharmaceutical composition to the subject.

In another aspect, methods of treating a subject are provided. In some embodiments, the subject has a condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause, such as vasomotor symptoms). In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising solubilized estradiol, suspended progesterone, and a solubilizing agent that comprises a medium chain (C6-C12) oil as described herein, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more pharmacokinetic parameters as described herein. In some embodiments, the method comprises administering a pharmaceutical composition comprising estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprising progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg. In some embodiments, the method comprises administering a pharmaceutical composition comprising: estradiol at a dosage of about 0.25 mg and progesterone at a dosage of about 50 mg; estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 50 mg; estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 100 mg; estradiol at a dosage of about 1 mg and progesterone at a dosage of about 100 mg; or estradiol at a dosage of about 2 mg and progesterone at a dosage of about 200 mg.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ( $AUC_{(0-t)}$ ) for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the pharmaceutical composition further produces, in a plasma sample from the subject, one or more parameters selected from: an  $AUC_{(0-t)}$  for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; a  $C_{max}$  for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; an  $AUC_{(0-t)}$  for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; and a  $C_{max}$  for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

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In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an  $AUC_{(0-t)}$  for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml and (b) a  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; and
- (ii) one or both of (a) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an  $AUC_{(0-t)}$  for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml and (b) a  $C_{max}$  for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; and optionally
- (iv) one or both of (a) an  $AUC_{(0-t)}$  for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml and (b) a  $C_{max}$  for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and
- (iv) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from: an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml and (b) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; and optionally
- (iii) one or both of (a) an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a) an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.



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In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ( $AUC_{(0-t)}$ ) for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from: an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, and a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml and (b) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; and
- (ii) one or both of (a) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally
- (iii) one or both of (a) an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml and (b) a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; and optionally
- (iv) one or both of (a)  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml and (b) a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an area under the curve ( $AUC_{(0-t)}$ ) for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and
- (iv) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from: an  $AUC_{(0-t)}$  for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml; a  $C_{max}$  for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; an  $AUC_{(0-t)}$  for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml; and a  $C_{max}$  for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

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In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, the following parameters:

- (i) one or both of (a) an  $AUC_{(0-t)}$  for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml and (b) a  $C_{max}$  for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; and
- (ii) one or both of (a) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml and (b) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; and optionally
- (iii) one or both of (a) an  $AUC_{(0-t)}$  for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml and (b) a  $C_{max}$  for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; and optionally
- (iv) one or both of (a) an  $AUC_{(0-t)}$  for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml and (b) a  $C_{max}$  for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

In still another aspect, pharmaceutical compositions for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency are provided. In some embodiments, the pharmaceutical composition comprises solubilized estradiol, suspended progesterone, and a solubilizing agent that comprises a medium chain (C6-C12) oil, wherein the treatment produces, in a plasma sample from the subject, one or more pharmacokinetic parameters as described herein (e.g., an  $AUC_{(0-t)}$  or  $C_{max}$  for estradiol, progesterone, estrone, or total estrone as described herein, e.g., as described in any of Tables 18-21). In some embodiments, the pharmaceutical compositions for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency comprise estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg, and comprise progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg.

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 0.25 mg and progesterone at a dosage of about 50 mg, and produces one or more pharmacokinetic values disclosed in Table 18 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 50 mg, and produces one or more pharmacokinetic values disclosed in Table 19 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 100 mg, and produces one or more pharmacokinetic values disclosed in Table 20 following administration of a

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single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

In some embodiments, a pharmaceutical composition for use in a method of treating a disease or condition that is caused at least in part by an estrogen deficiency (e.g., one or more symptoms of menopause) comprises estradiol at a dosage of about 1 mg and progesterone at a dosage of about 100 mg, and produces one or more pharmacokinetic values disclosed in Table 21 following administration of a single dose of the pharmaceutical composition to a subject (e.g., about 24 hours or about 48 hours after administration).

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates a semilogarithmic plot of mean plasma concentration (pg/ml) over time (hrs) for estradiol.

FIG. 2 illustrates a semilogarithmic plot of mean plasma concentration (ng/ml) over time (hrs) for progesterone.

FIG. 3 illustrates a semilogarithmic plot of mean plasma concentration (pg/ml) over time (hrs) for estrone.

FIG. 4 illustrates a semilogarithmic plot of mean plasma concentration (ng/ml) over time (hrs) for total estrone.

#### DETAILED DESCRIPTION OF THE INVENTION

In the following detailed description of embodiments of this disclosure, reference is made to the accompanying drawings in which like references indicate similar elements, and in which is shown, by way of illustration, specific embodiments in which this disclosure may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice this disclosure, and it is to be understood that other embodiments may be utilized and that other changes may be made without departing from the scope of this disclosure. The following detailed description is, therefore, not to be taken in a limiting sense, and the scope of this disclosure is defined only by the appended claims. As used in this disclosure, the term “or” shall be understood to be defined as a logical disjunction (i.e., and/or) and shall not indicate an exclusive disjunction unless expressly indicated as such with the term “either,” “unless,” “alternatively,” and words of similar effect.

#### I. DEFINITIONS

The term “area under the curve” (“AUC”) refers to the area under the curve defined by changes in the blood, plasma, or serum concentration of an active pharmaceutical ingredient (e.g., estradiol or progesterone), or one or more metabolites of the active pharmaceutical ingredient, over time following the administration of a dose of the active pharmaceutical ingredient. “AUC<sub>0-∞</sub>” is the area under the concentration-time curve extrapolated to infinity following the administration of a dose. “AUC<sub>0-t</sub>” is the area under the concentration-time curve from time zero to time t following the administration of a dose, wherein t is the last time point with measurable concentration.

The term “C<sub>max</sub>” refers to the maximum value of blood, plasma, or serum concentration shown on the curve that represents changes in blood, plasma, or serum concentrations of an active pharmaceutical ingredient (e.g., progesterone or estradiol), or one or more metabolites of the active pharmaceutical ingredient, over time.

The term “T<sub>max</sub>” refers to the time that it takes for the blood, plasma, or serum concentration of an active pharma-

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ceutical ingredient (e.g., estradiol or progesterone), or of one or more metabolites of the active pharmaceutical ingredient, to reach the maximum value.

Collectively, AUC, C<sub>max</sub>, and, optionally, T<sub>max</sub> are the principal pharmacokinetic parameters that can characterize the pharmacokinetic response of a particular drug product, such as progesterone or estradiol, in an animal, especially a mammal, including human, subject.

An “active pharmaceutical ingredient” (API), as used herein, means the active compound or compounds used in formulating a drug product. APIs are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “bioavailability” has the meaning as defined in 21 C.F.R. § 320.1(a): the rate and extent to which an API or active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the API or active ingredient or active moiety becomes available at the site of action. For example, bioavailability can be measured as the amount of API in the blood (whole blood, serum, or plasma) as a function of time. In embodiments, the amount of API is measured in blood plasma. Pharmacokinetic (PK) parameters such as AUC, C<sub>max</sub>, or T<sub>max</sub> may be used to measure and assess bioavailability.

The term “bioequivalent” has the meaning as defined in 21 C.F.R. § 320.1(e): the absence of a significant difference in the rate and extent to which the API or active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended release dosage forms or modified release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. In practice, two products are considered bioequivalent if the 90% confidence interval of the AUC, C<sub>max</sub>, or optionally T<sub>max</sub> is within 80.00% to 125.00%.

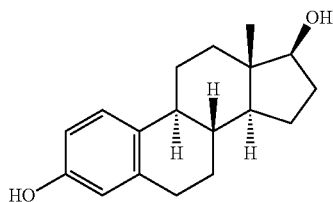
The term “bio-identical hormone” or “body-identical hormone” refers to an active pharmaceutical ingredient that is structurally identical to a hormone naturally or endogenously found in the human body (e.g., estradiol and progesterone).

The term “estrogen” refers to a group of several female sex hormones produced primarily by the ovaries, including estradiol, estrone, and estrinol. As used herein, unless otherwise specified, estrogen refers to estradiol.

The term “estradiol” refers to (17β)-estra-1,3,5(10)-triene-3,17-diol. Estradiol is also interchangeably called 17β-estradiol, oestradiol, or E2, and is found endogenously in the human body. As used herein, estradiol refers to the bio-identical or body-identical form of estradiol found in the human body having the structure:

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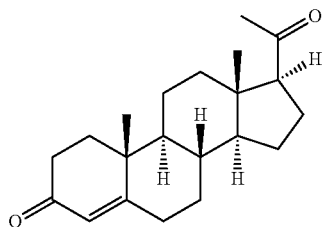
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As used herein, unless specified, estradiol includes estradiol in anhydrous or hemi-hydrate forms. For the purposes of this disclosure, the anhydrous form or the hemihydrate form can be substituted for the other by accounting for the water or lack of water according to well-known and understood techniques.

The term “solubilized estradiol” means that the estradiol or a portion thereof is solubilized or dissolved in the solubilizing agents or the formulations disclosed herein. Solubilized estradiol may include estradiol that is about 80% solubilized, about 85% solubilized, about 90% solubilized, about 95% solubilized, about 96% solubilized, about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. In some embodiments, the estradiol is “fully solubilized” with all or substantially all of the estradiol being solubilized or dissolved in the solubilizing agent. Fully solubilized estradiol may include estradiol that is about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. Solubility can be expressed as a mass fraction (% w/w, which is also referred to as wt %).

The term “progesterone” refers to pregn-4-ene-3,20-dione. Progesterone is also interchangeably called P4 and is found endogenously in the human body. As used herein, progesterone refers to the bio-identical or body-identical form of progesterone found in the human body having the structure:



The term “solubilized progesterone” means that the progesterone or a portion thereof is solubilized or dissolved in the solubilizing agents or the formulations disclosed herein. In some embodiments, the progesterone is “partially solubilized” with a portion of the progesterone being solubilized or dissolved in the solubilizing agent and a portion of the progesterone being suspended in the solubilizing agent. Partially solubilized progesterone may include progesterone that is about 1% solubilized, about 5% solubilized, about 10% solubilized, about 15% solubilized, about 20% solubilized, about 30% solubilized, about 40% solubilized, about 50% solubilized, about 60% solubilized, about 70% solubilized, about 80% solubilized, about 85% solubilized, about 90% solubilized or about 95% solubilized. In other embodiments, the progesterone is “fully solubilized” with all or substantially all of the progesterone being solubilized or dissolved in the solubilizing agent. Fully solubilized progesterone may include progesterone

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that is about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. Solubility can be expressed as a mass fraction (% w/w, which is also referred to as wt %).

The terms “micronized progesterone” and “micronized estradiol,” as used herein, include micronized progesterone and micronized estradiol, respectively, having an X50 particle size value below about 15 microns or having an X90 particle size value below about 25 microns. The term “X50” means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term “X90” means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The term “solubilizing agent” refers to an agent or combination of agents that solubilize an active pharmaceutical ingredient (e.g., estradiol or progesterone). For example and without limitation, suitable solubilizing agents include medium chain oils and other solvents and co-solvents that solubilize or dissolve an active pharmaceutical ingredient to a desirable extent. Solubilizing agents suitable for use in the formulations disclosed herein are pharmaceutical grade solubilizing agents (e.g., pharmaceutical grade medium chain oils). It will be understood by those of skill in the art that other excipients or components can be added to or mixed with the solubilizing agent to enhance the properties or performance of the solubilizing agent or resulting formulation. Examples of such excipients include, but are not limited to, surfactants, emulsifiers, thickeners, colorants, flavoring agents, etc. In some embodiments, the solubilizing agent is a medium chain oil and, in some other embodiments, the medium chain oil is combined with a co-solvent(s) or other excipient(s).

The term “medium chain” is used to describe the aliphatic chain length of fatty acid containing molecules. “Medium chain” specifically refers to fatty acids, fatty acid esters, or fatty acid derivatives that contain fatty acid aliphatic tails or carbon chains that contain between 6 (C6) and 14 (C14) carbon atoms.

The terms “medium chain fatty acid” and “medium chain fatty acid derivative” are used to describe fatty acids or fatty acid derivatives with aliphatic tails (i.e., carbon chains) having 6 to 14 carbons. Fatty acids consist of an unbranched aliphatic tail attached to a carboxylic acid functional group. Fatty acid derivatives include, for example, fatty acid esters and fatty acid containing molecules, including, without limitation, mono-, di- and triglycerides that include components derived from fatty acids as well as fatty acid esters of ethylene or propylene glycol. Those of skill will appreciate that the aliphatic tails can be saturated or unsaturated (one or more double bonds between carbon atoms). In some embodiments, the aliphatic tails are saturated (i.e., no double bonds between carbon atoms). Medium chain fatty acids or medium chain fatty acid derivatives include those with aliphatic tails having 6-14 carbons, including those that are C6-C14, C6-C12, C8-C14, C8-C12, C6-C10, C8-C10, or others. In embodiments, medium chain fatty acids or medium chain fatty acid derivatives are those that are saturated. Examples include, without limitation, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, and derivatives thereof.

The term “oil,” as used herein, refers to any pharmaceutically acceptable oil, and specifically excluding peanut oil, that can suspend or solubilize any suitable progesterone or

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estradiol, starting material, or precursor, including micronized progesterone or estradiol as described herein.

The term “medium chain oil” refers to an oil wherein the composition of the fatty acid fraction of the oil is substantially medium chain (i.e., C6 to C14) fatty acids, i.e., the composition profile of fatty acids in the oil is substantially medium chain. As used herein, “substantially” means that between 20% and 100% (inclusive of the upper and lower limits) of the fatty acid fraction of the oil is made up of medium chain fatty acids, i.e., fatty acids with aliphatic tails (i.e., carbon chains) having 6 to 14 carbons. In some embodiments, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 85%, about 90% or about 95% of the fatty acid fraction of the oil is made up of medium chain fatty acids. Those of skill in the art that will readily appreciate that the terms “alkyl content” or “alkyl distribution” of an oil can be used in place of the term “fatty acid fraction” of an oil in characterizing a given oil or solubilizing agent, and these terms are used interchangeable herein. As such, medium chain oils suitable for use in the formulations disclosed herein include medium chain oils wherein the fatty acid fraction of the oil is substantially medium chain fatty acids, or medium chain oils wherein the alkyl content or alkyl distribution of the oil is substantially medium chain alkyls (C6-C12 alkyls). It will be understood by those of skill in the art that the medium chain oils suitable for use in the formulations disclosed herein are pharmaceutical grade (e.g., pharmaceutical grade medium chain oils). Examples of medium chain oils include, for example and without limitation, medium chain fatty acids, medium chain fatty acid esters of glycerol (e.g., for example, mono-, di-, and triglycerides), medium chain fatty acid esters of propylene glycol, medium chain fatty acid derivatives of polyethylene glycol, and combinations thereof.

The term “ECN” or “equivalent carbon number” means the sum of the number of carbon atoms in the fatty acid chains of an oil, and can be used to characterize an oil as, for example, a medium chain oil or a long-chain oil. For example, tripalmitin (tripalmitic glycerol), which is a simple triglyceride containing three fatty acid chains of 16 carbon atoms, has an ECN of  $3 \times 16 = 48$ . Conversely, a triglyceride with an ECN=40 may have “mixed” fatty acid chain lengths of 8, 16, and 16; 10, 14, and 16; 8, 14, and 18; etc. Naturally occurring oils are frequently “mixed” with respect to specific fatty acids, but tend not to contain both long chain fatty acids and medium chain fatty acids in the same glycerol backbone. Thus, triglycerides with ECNs of 21-42 typically contain predominantly medium chain fatty acids; while triglycerides with ECNs of greater than 43 typically contain predominantly long chain fatty acids. For example, the ECN of corn oil triglyceride in the US Pharmacopeia (USP) would be in the range of 51-54. Medium chain diglycerides with ECNs of 12-28 will often contain predominantly medium chain fatty acids, while diglycerides with ECNs of 32 or greater will typically contain predominantly long chain fatty acids. Monoglycerides will have an ECN that matches the chain length of the sole fatty acid chain. Thus, monoglyceride ECNs in the range of 6-14 contain mainly medium chain fatty acids, and monoglycerides with ECNs 16 or greater will contain mainly long chain fatty acids.

The average ECN of a medium chain triglyceride oil is typically 21-42. For example, as listed in the USP, medium chain triglycerides have the following composition as the exemplary oil set forth in the table below:

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Fatty Acid Tail Length	% of Oil	Exemplary Oil
6	≤2.0	2.0
8	50.0-80.0	70.0
10	20.0-50.0	25.0
12	≤3.0	2.0
14	≤1.0	1.0

and would have an average ECN of  $3 \times [(6 \times 0.02) + (8 \times 0.070) + (10 \times 0.25) + (12 \times 0.02) + (14 \times 0.01)] = 25.8$ . The ECN of the exemplary medium chain triglycerides oil can also be expressed as a range (per the ranges set forth in the USP) of 24.9-27.0. For oils that have mixed mono-, di-, and triglycerides, or single and double fatty acid glycols, the ECN of the entire oil can be determined by calculating the ECN of each individual component (e.g., C8 monoglycerides, C8 diglycerides, C10 monoglycerides, and C10 diglycerides) and taking the sum of the relative percentage of the component multiplied by the ECN normalized to a monoglyceride for each component. For example, the oil having C8 and C10 mono- and diglycerides shown in the table below has an ECN of 8.3, and is thus a medium chain oil:

Fatty Acid Chain Length	% of Oil	ECN as % of Oil [(chain length) × (% in oil)]	ECN as % of Oil Normalized to Monoglyceride
C8 monoglyceride	47	$8 \times 0.47 = 3.76$	3.76
C10 monoglyceride	8	$10 \times 0.08 = 0.8$	0.8
C8 diglyceride	38	$2 \times (8 \times 0.38) = 6.08$	$6.08/2 = 3.04$
C10 diglyceride	7	$2 \times (10 \times 0.07) = 1.4$	$1.4/2 = 0.7$
OIL ECN (normalized to monoglycerides)			8.3

Expressed differently, ECN can be calculated as each chain length in the composition multiplied by its relative percentage in the oil:  $(8 \times 0.85) + (10 \times 0.15) = 8.3$ .

The term “excipients,” as used herein, refers to non-active pharmaceutical ingredients such as solubilizing agents, antioxidants, oils, lubricants, and others used in formulating pharmaceutical products.

The terms “treat,” “treating,” and “treatment” refer to any indicia of success in the treatment or amelioration of an injury, disease, or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, disease, or condition more tolerable to the patient; slowing in the rate of degeneration or decline; or improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subject parameters, including the results of a physical examination, neuropsychiatric examinations, or psychiatric evaluation.

## II. PHARMACEUTICAL COMPOSITIONS

In one aspect, this disclosure relates to pharmaceutical compositions for co-administering estradiol and progesterone to a human subject in need thereof. In some embodiments, the composition comprises estradiol, progesterone, and a solubilizing agent (e.g., a medium chain oil, e.g., a C6-C12 oil). In some embodiments, a pharmaceutical composition comprising estradiol, progesterone, and a solubilizing agent as described herein, when administered to a subject or a population of subjects, produces one or more AUC,  $C_{max}$ , or  $T_{max}$  parameters for estradiol, progesterone, estrone, or total estrone as described below.



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## Formulations of Estradiol and Progesterone Compositions

In some embodiments, a pharmaceutical composition for use as described herein comprises solubilized estradiol with suspended progesterone; solubilized estradiol with both partially solubilized progesterone and partially suspended progesterone; or solubilized estradiol with fully solubilized progesterone. In some embodiments, the composition comprises solubilized estradiol and suspended progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone, although the natural or bio-identical forms of estradiol and progesterone are preferred.

In some embodiments, the composition comprises estradiol at a dosage of about 0.05, 0.1, 0.125, 0.15, 0.20, 0.25, 0.30, 0.35, 0.375, 0.40, 0.45, 0.50, 0.55, 0.60, 0.625, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75, or 2.00 mg. In some embodiments, the composition comprises progesterone at a dosage of about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg.

In some embodiments, estradiol is solubilized. Solubilized estradiol may include estradiol that is approximately 80% to 100% soluble in a solubilizing agent, including specifically embodiments that are: 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% soluble in a solubilizing agent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %). In some embodiments, estradiol is micronized. In some embodiments, micronized estradiol has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns or less than about 3 microns. In some embodiments, micronized estradiol has an X90 particle size value of less than about 25 microns, less than about 20 microns, or less than about 15 microns. In some embodiments, the composition comprises micronized and partially solubilized estradiol.

In some embodiments, the composition comprises micronized progesterone. The progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, or less than about 15 microns. Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size.

Estradiol and progesterone compositions and methods of preparing such compositions are described in U.S. Pat. No. 8,633,178; U.S. Publication No. 2013/0129818; U.S. Publication No. 2013/0338123; International Publication No. WO 2013/078422; and International Publication No. WO 2013/192251; each of which is incorporated by reference in its entirety.

## Solubilizing Agents

Estradiol and progesterone compositions of the present disclosure are prepared via blending with a solubilizing agent. In some embodiments, the solubilizing agent is a pharmaceutically acceptable oil that comprises a medium chain oil. In some embodiments, the solubilizing agent is a medium chain oil comprised substantially of C6-C12 medium chains, e.g., at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at

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least 90% of the chains present in the oil are C6-C12. In some embodiments, the oil comprises at least one medium chain fatty acid such as medium chain fatty acids having at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. In some embodiments, the medium chain oil comprises at least one medium chain fatty acid or propylene glycol, polyethylene glycol, or glyceride having esters of medium chain fatty acids. In some embodiments, the solubilizing agent is not peanut oil.

In some embodiments, oils used to solubilize estradiol and to suspend, partially suspend and partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In some embodiments, the medium chain fatty acids are C6, C8, C10, C12, C6-C12, C8-C12, C6-C10, C8-C10, or C10-C12 fatty acids. In some embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 50% saturated, greater than about 60% saturated, or greater than about 75% saturated. In some embodiments, a solubilizing agent comprises predominantly medium chain length, saturated fatty acids or derivatives thereof, specifically predominantly C8 to C12 saturated fatty acids or derivatives thereof.

In some embodiments, medium chain solubilizing agents include, for example and without limitation, saturated medium chain fatty acids or derivatives of saturated medium chain fatty acids: caproic acid (C6), enanthic acid (C7), caprylic acid (C8), pelargonic acid (C9), capric acid (C10), undecylic acid (C11), lauric acid (C12), tridecylic acid (C13), or myristic acid (C14). In some embodiments, the solubilizing agent comprises oils made of these free medium chain fatty acids, oils of medium chain fatty acid esters of glycerin, propylene glycol, or ethylene glycol, or combinations thereof. These examples comprise predominantly saturated medium chain fatty acids (i.e., greater than 50% of the fatty acids are medium chain saturated fatty acids). In some embodiments, the solubilizing agent comprises predominantly C6 to C12 saturated fatty acids or derivatives of fatty acids.

In some embodiments, the solubilizing agent comprises one or more mono-, di-, or triglycerides or combinations thereof. Exemplary glycerin based solubilizing agents include MIGLYOLs®, which are caprylic/capric triglycerides (SASOL Germany GMBH, Hamburg). MIGLYOLs® includes MIGLYOL® 810 (caprylic/capric triglyceride), MIGLYOL® 812 (caprylic/capric triglyceride), MIGLYOL® 816 (caprylic/capric triglyceride), and MIGLYOL® 829 (caprylic/capric/succinic triglyceride). Other caprylic/capric triglyceride solubilizing agents are likewise contemplated, including, for example: caproic/caprylic/capric/lauric triglycerides; caprylic/capric/linoleic triglycerides; or caprylic/capric/succinic triglycerides. Other exemplary caprylic/capric mono-, di-, or triglyceride solubilizing agents include CAPMULs® (ABITEC, Columbus, Ohio), including, but are not limited to, CAPMUL® MCM, CAPMUL® MCM C10, CAPMUL® MCM C8, CAPMUL® MCM C8 EP, and CAPMUL® 708 G. Other mono-, di-, and triglycerides of fractionated vegetable fatty acids, and combinations or derivatives thereof can be the solubilizing agent, according to embodiments. For example, the solubilizing agent can be 1,2,3-propanetriol (glycerol, glycerin, glycerine) esters of saturated coconut and palm kernel oil and derivatives thereof.

In some embodiments, the solubilizing agent comprises one or more esters of propylene glycol, polyethylene glycol, or combinations thereof. Exemplary propylene and polyeth-

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ylene glycol based solubilizing agents include glyceryl mono- and di-caprylates; propylene glycol monocaprylate (e.g., CAPMUL® PG-8 or CAPMUL® PG-8 NF); propylene glycol monocaprate (e.g., CAPMUL® PG-10); propylene glycol monolaurate (e.g., CAPMUL® PG-12 EP/NF); propylene glycol mono- and dicaprylates; propylene glycol mono- and dicaprate; propylene glycol dicaprylate/dicaprate (e.g., MIGLYOL® 840); propylene glycol dilaurate (e.g., CAPMUL® PG-2L EP/NF); diethylene glycol mono ester (e.g., TRANSCUTOL®, 2-(2-Ethoxyethoxyl)ethanol, GATTEFOSSÉ SAS, Saint-Priest, France); and diethylene glycol monoethyl ether.

In some embodiments, commercially available fatty acid glycerol and glycol ester solubilizing agents are prepared from natural oils and therefore may comprise components in addition to the fatty acid esters that predominantly comprise and characterize the solubilizing agent. Such other components may be, e.g., other fatty acid mono-, di-, and triglycerides, fatty acid mono- and diester ethylene or propylene glycols, free glycerols or glycols, or free fatty acids. For example, the Technical Data Sheet by ABITEC for CAPMUL® MCM C8 describes CAPMUL® MCM C8 as being composed of mono- and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as  $\leq 1\%$  C6,  $\geq 95\%$  C8,  $\leq 5\%$  C10, and  $\leq 1.5\%$  C12 and higher. By way of further example, MIGLYOL® 812 is generally described as a C8-C10 triglyceride because the fatty acid composition is at least about 80% caprylic (C8) acid and capric (C10) acid. However, it can also comprise small amounts of other fatty acids, e.g., less than about 5% of caproic (C6) acid, lauric (C12) acid, and myristic (C14) acid.

In some embodiments, the pharmaceutical composition comprises about 20% to about 85% solubilizing agent by weight, e.g., about 60% to about 85% solubilizing agent by weight. In some embodiments, the composition comprises progesterone, e.g., dissolved and micronized, from about 20 to about 50 wt %, e.g., about 30 to about 35 wt %. In some embodiments, the composition comprises estradiol from about 0.1 to about 0.8 wt %, e.g., about 0.15 to about 0.40 wt %.

#### Surfactants

In some embodiments, the pharmaceutical composition further comprises one or more non-ionic or ionic surfactants. In some embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of medium chain fatty acids or long chain fatty acids, for example, lauroyl macrogol-32 glycerides or lauroyl polyoxyl-32 glycerides, commercially available as GELUCIRE®, including, for example, GELUCIRE® 39/01 (glycerol esters of saturated C12-C18 fatty acids); GELUCIRE® 43/01 (hard fat NF/JPE); GELUCIRE® 44/14 (lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides NF, lauroyl polyoxylglycerides (USA FDA IIG)); and GELUCIRE® 50/13 (stearoyl macrogol-32 glycerides EP, stearoyl polyoxyl-32 glycerides NF, stearoyl polyoxylglycerides (USA FDA IIG)).

In some embodiments, non-ionic surfactants comprise combinations of mono- and di-propylene and ethylene glycols and mono-, di-, and triglyceride combinations. For example, in some embodiments, polyethylene glycol glyceride (GELUCIRE®, GATTEFOSSÉ SAS, Saint-Priest, France) can be used herein as the surfactant. For example, GELUCIRE® 44/14 (PEG-32 glyceryl laurate EP), a medium chain fatty acid esters of polyethylene glycol, is a polyethylene glycol glyceride composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

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In some embodiments, non-ionic surfactants include, for example and without limitation: one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid. In some embodiments, non-ionic surfactants comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids.

In some embodiments, non-ionic surfactants include PEG-6 palmitostearate and ethylene glycol palmitostearate, which are available commercially as TEFOSE® 63 (GATTEFOSSÉ SAS, Saint-Priest, France), which can be used with, for example, CAPMUL® MCM having ratios of MCM to TEFOSE® 63 of, for example, 8:2 or 9:1. Other exemplary solubilizing agents/non-ionic surfactants combinations include, without limitation: MIGLYOL® 812:GELUCIRE 50/13 or MIGLYOL® 812:TEFOSE® 63.

A non-ionic or ionic surfactant may be used at concentrations greater than about 0.01%, for example at a concentration of about 0.01%-10.0%, about 0.1% to 10.0%, or about 1% to 10.0%. In some embodiments, the pharmaceutical composition comprises about 10.0% surfactant by weight. In some embodiments, the pharmaceutical composition comprises about 0.1% to about 5.0% surfactant by weight, e.g., about 1.0 wt %.

#### Other Excipients

In some embodiments, the pharmaceutical composition further comprises one more other excipients, such as but not limited to colorants, flavoring agents, preservatives, and taste-masking agents. The choice of excipients will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipients on solubility and stability, and the nature of the dosage form. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

Generally, the solubilizing agents, surfactants, and excipients used in the pharmaceutical compositions described herein are non-toxic, pharmaceutically acceptable, compatible with each other, and maintain stability of the pharmaceutical composition and the various components with respect to each other. Additionally, the combination of various components that comprise the pharmaceutical compositions will maintain will result in the desired therapeutic effect when administered to a subject.

#### Formulation

In some embodiments, combinations of solubilizing agents (e.g., two or more oils) or combinations of one or more solubilizing agents and one or more surfactants are used to form estradiol and progesterone compositions. Various ratios of these solubilizing agents or solubilizing agents and surfactants can be used. For example, CAPMUL® MCM and a non-ionic surfactant, e.g., GELUCIRE® 44/14 (lauroyl macrogol-32 glycerides EP; lauroyl polyoxyl-32 glycerides NF; lauroyl polyoxylglycerides (USA FDA IIG)), can be used at ratios of about 99:1 to about 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. As another example, CAPMUL® MCM and a non-ionic surfactant, e.g., TEFOSE® 63, can be used as ratios of about 8:2 or 9:1. Other exemplary solubilizing agent/surfactant combinations include, without limitation: MIGLYOL® 812:GELUCIRE® 50/13 or MIGLYOL® 812:TEFOSE® 63. The ratios of oil (e.g., medium chain fatty acid esters of mono-glycerides and diglycerides) to non-ionic surfactant can be



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significantly higher. For example, CAPMUL® MCM and GELUCIRE® can be used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1.

In some embodiments, estradiol or progesterone is soluble in the solubilizing agent at room temperature, although it may be desirable to warm certain solubilizing agents. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., CAPMUL® MCM) and polyethylene glycol glycerides (e.g., GELUCIRE®) as a surfactant, the oil or the surfactant can be warmed up, e.g., to about 65° C. for the surfactant and less for the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature, or at lower temperatures as the mixture cools, e.g., about 40° C. or about 30° C., or even after the mixture has cooled to room temperature. The progesterone can also be added as the mixture cools, e.g., to below about 40° C. or to below about 30° C., or after the mixture has cooled to room temperature.

As a non-limiting example, a composition of this disclosure comprises solubilized estradiol; progesterone, at least 30% (e.g., at least about 30%, about 40%, about 50%, about 60%, about 70%, about 75%, about 80%, about 85%, or more) of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein); and a solubilizing agent that is an oil, wherein the oil comprises medium chain fatty acid mono-, di-, or triglycerides, with or without a surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with CAPMUL® MCM NF (glyceryl caprylate/caprate) as a solubilizing agent and GELUCIRE® 44/14 (lauroyl polyoxyglyceride) as a surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following five formulations A-E:

TABLE 1

Pharmaceutical Composition A - progesterone 50 mg/estradiol 0.25 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.17	0.26
CAPMUL ® MCM, NF	65.49	98.24
GELUCIRE ® 44/14, NF	1.00	1.50
Total	100.00	150.00

TABLE 2

Pharmaceutical Composition B - progesterone 50 mg/estradiol 0.5 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.35	0.52
CAPMUL ® MCM, NF	65.32	97.98
GELUCIRE ® 44/14, NF	1.00	1.50
Total	100.00	150.00

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TABLE 3

Pharmaceutical Composition C - progesterone 100 mg/estradiol 0.5 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.17	0.52
CAPMUL ® MCM, NF	65.49	196.48
GELUCIRE ® 44/14, NF	1.00	3.00
Total	100.00	300.00

TABLE 4

Pharmaceutical Composition D - progesterone 100 mg/estradiol 1 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.34	1.03
CAPMUL ® MCM, NF	65.32	195.97
GELUCIRE ® 44/14, NF	1.00	3.00
Total	100.00	300.00

\*Note:

1.00 mg Estradiol is equivalent to 1.03 mg Estradiol Hemihydrate

TABLE 5

Pharmaceutical Composition E - progesterone 200 mg/estradiol 2 mg		
Ingredient	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate	0.34	2.06
CAPMUL ® MCM, NF	65.32	391.94
GELUCIRE ® 44/14, NF	1.00	6.00
Total	100.00	600.00

In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono-, di-, or triglycerides, such as CAPMUL® MCM, and 0.5 to 10 wt % of a non-ionic surfactant, such as GELUCIRE® 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opaint red and white, and, optionally, MIGLYOL® 812.

Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g., at least about 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% or more, is solubilized appear to provide improved PK-related properties.

Pharmacokinetic Parameters of Estradiol and Progesterone Compositions

The pharmaceutical compositions of this disclosure can be formulated to provide desirable pharmacokinetic parameters in a subject (e.g., a female subject) to whom the composition is administered. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for progesterone in the

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subject. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for estradiol in the subject. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for one or more metabolites of progesterone or estradiol in the subject, for example, estrone or total estrone.

Following the administration of a composition comprising progesterone and estradiol to a subject, the concentration and metabolism of progesterone or estradiol can be measured in a sample (e.g., a blood, serum, or plasma sample) from the subject. Progesterone is metabolized to pregnanediols and pregnanones, which are then conjugated to glucuronide and sulfate metabolites that are excreted or further recycled. Estradiol is converted reversibly to estrone, and both estradiol and estrone can be converted to the metabolite estriol. In postmenopausal women, a significant proportion of circulating estrogens exist as sulfate conjugates, especially estrone sulfate. Thus, estrone can be measured with respect to "estrone" amounts (excluding conjugates such as estrone sulfate) and "total estrone" amounts (including both free, or unconjugated, estrone and conjugated estrone such as estrone sulfate).

The pharmaceutical compositions of this disclosure can be characterized for one or more pharmacokinetic parameters of progesterone, estradiol, or a metabolite thereof following administration of the composition to a subject or to a population of subjects. These pharmacokinetic parameters include AUC,  $C_{max}$ , and  $T_{max}$ . AUC is a determination of the area under the curve (AUC) plotting the blood, serum, or plasma concentration of drug along the ordinate (Y-axis) against time along the abscissa (X-axis). AUCs are well understood, frequently used tools in the pharmaceutical arts and have been extensively described.  $C_{max}$  is well understood in the art as an abbreviation for the maximum drug concentration in blood, serum, or plasma of a subject.  $T_{max}$  is well understood in the art as an abbreviation for the time to maximum drug concentration in blood, serum, or plasma of a subject.

In some embodiments, one or more pharmacokinetic parameters, e.g., AUC,  $C_{max}$ , or  $T_{max}$ , is measured for estradiol. In some embodiments, one or more pharmacokinetic parameters, e.g., AUC,  $C_{max}$ , or  $T_{max}$ , is measured for progesterone. In some embodiments, one or more pharmacokinetic parameters, e.g., AUC,  $C_{max}$ , or  $T_{max}$ , is measured for estrone. In some embodiments, one or more pharmacokinetic parameters, e.g., AUC,  $C_{max}$ , or  $T_{max}$ , is measured for total estrone.

Any of a variety of methods can be used for measuring the levels of progesterone, estradiol, estrone, or total estrone in a sample, including immunoassays, mass spectrometry (MS), high performance liquid chromatography (HPLC) with ultraviolet fluorescent detection, liquid chromatography in conjunction with mass spectrometry (LC-MS), tandem mass spectrometry (MS/MS), and liquid chromatography-tandem mass spectrometry (LC-MS/MS). In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured using a validated LC-MS/MS method. Methods of measuring hormone levels are well described in the literature.

The levels of progesterone, estradiol, estrone, or total estrone can be measured in any biological sample, e.g. a tissue or fluid such as blood, serum, plasma, or urine. In some embodiments, the sample is blood or plasma. In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured about 0.0, 0.10, 0.20, 0.05, 0.30, 0.35, 0.40, 0.45, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15,

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18, 21, 24, 27, 30, 33, 36, 39, 42, 45, or 48 hours after dosing, or any other appropriate time period that is common or useful in determining the levels of each of the hormones. In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of a single dose or a first dose. Generally, assays to determine the levels of progesterone, estradiol, estrone, or total estrone are measured one or more times every 5, 10, 15, 20, 30, 60, 120, 360, 480, 720, or 1440 minutes after administration, or combinations thereof (e.g., the first measurements are taken every 15 minutes for the first hour, followed by every 120 minutes thereafter). In embodiments, the timing of such measurements are designed to accurately measure  $C_{max}$ ,  $T_{max}$ , or AUC. Timing can be adjusted based on the given circumstances (i.e., one formulation may cause a more rapid  $C_{max}$ , in which case the initial times would be clustered closer together, closer to time zero, or both to ensure accurate measurement of  $C_{max}$ ,  $T_{max}$ , and AUC). In some embodiments, the  $C_{max}$ ,  $T_{max}$ , or AUC values for progesterone, estradiol, estrone, or total estrone are measured following administration of a single dose of a pharmaceutical composition as described herein.

In some embodiments, the values for  $C_{max}$ ,  $T_{max}$ , or AUC represent a number of values taken from all the subjects in a patient population and are, therefore, mean values (e.g., arithmetic or geometric means) averaged over the entire population.

In some embodiments, oral administration of a pharmaceutical composition comprising estradiol, progesterone, and a medium chain solubilizing agent as described herein to a subject, or to a population of subjects, produces one or more AUC,  $C_{max}$ , or  $T_{max}$  parameters, or one or more mean AUC, mean  $C_{max}$ , or mean  $T_{max}$  parameters, respectively, for estradiol, progesterone, estrone, or total estrone as described below.

#### AUC $C_{max}$ , and $T_{max}$ Parameters (A)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 0.25 mg and progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation A in Table 1 above.

In some embodiments, administration of a composition comprising about 0.25 mg estradiol and about 50 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; or
- (ii) a  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

In some embodiments, administration of the composition to the subject produces both an  $AUC_{(0-t)}$  for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml, and a  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (ii) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces both an  $AUC_{(0-t)}$  for progesterone

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that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, and a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml;
- (ii) a  $C_{max}$  for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; or
- (iii) a  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml;

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- (ii) a  $C_{max}$  for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml; or

- (iii) a  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml, a mean  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml, and a mean  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, a mean  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml, and a mean  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml, a mean  $C_{max}$  for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml, and a mean  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml, a mean  $C_{max}$  for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml, and a mean  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, methods of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.25 mg estradiol and about 50 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation A in Table 1 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an  $AUC_{(0-t)}$  for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; a  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; a  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr; an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; a  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr; an  $AUC_{(0-t)}$  for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; a  $C_{max}$  for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; a  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr; an  $AUC_{(0-t)}$  for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; a  $C_{max}$  for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml; and a  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation A in Table 1 above), and measuring one or more pharmacokinetic parameters selected from an  $AUC_{(0-t)}$  for estradiol, a  $C_{max}$  for estradiol, an  $AUC_{(0-t)}$  for progesterone, a  $C_{max}$  for progesterone, an  $AUC_{(0-t)}$  for estrone, a  $C_{max}$  for estrone, an  $AUC_{(0-t)}$  for total estrone, and a  $C_{max}$  for total estrone;

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wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an  $AUC_{(0-t)}$  for estradiol that is from 140.3733 pg·hr/ml to 219.3333 pg·hr/ml; a  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml; an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; an  $AUC_{(0-t)}$  for estrone that is from 909.6091 pg·hr/ml to 1421.2642 pg·hr/ml; a  $C_{max}$  for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml; an  $AUC_{(0-t)}$  for total estrone that is from 20.1752 ng·hr/ml to 31.5238 ng·hr/ml; or a  $C_{max}$  for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

$AUC$ ,  $C_{max}$ , and  $T_{max}$  Parameters (B)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 50 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation B in Table 2 above.

In some embodiments, administration of a composition comprising about 0.50 mg estradiol and about 50 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; or
- (ii) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject produces both an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, and a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (ii) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces both an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, and a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr.

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In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; or
- (iv) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml;
- (ii) a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; or
- (iii) a  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml;
- (ii) a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; or
- (iii) a  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, a mean  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml, and a mean  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml, a mean  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819



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ng/ml, and a mean  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, a mean  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml, and a mean  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, a mean  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml, and a mean  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, methods of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 50 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation B in Table 2 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; a  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr; an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; a  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr; an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; a  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr; an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; and a  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation B in Table 2 above), and measuring one or more pharmacokinetic parameters selected from an  $AUC_{(0-t)}$  for estradiol, a  $C_{max}$  for estradiol, an  $AUC_{(0-t)}$  for progesterone, a  $C_{max}$  for progesterone, an  $AUC_{(0-t)}$  for estrone, a  $C_{max}$  for estrone, an  $AUC_{(0-t)}$  for total estrone, and a  $C_{max}$  for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml; an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

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$AUC$ ,  $C_{max}$ , and  $T_{max}$  Parameters (C)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 0.50 mg and progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation C in Table 3 above.

In some embodiments, administration of a composition comprising about 0.50 mg estradiol and about 100 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; or
- (ii) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject produces both an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, and a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (ii) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces both an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, and a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the

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subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml;
- (ii) a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; or
- (iii) a  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml;
- (ii) a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; or
- (iii) a  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood and plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml, a mean  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml, and a mean  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, a mean  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml, and a mean  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml, a mean  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml, and a mean  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml, a mean  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml, and a mean  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, method of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 0.50 mg estradiol and about 100 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation

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C in Table 3 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; a  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr; an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; a  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr; an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; a  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr; an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml; and a  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation C in Table 3 above), and measuring one or more pharmacokinetic parameters selected from an  $AUC_{(0-t)}$  for estradiol, a  $C_{max}$  for estradiol, an  $AUC_{(0-t)}$  for progesterone, a  $C_{max}$  for progesterone, an  $AUC_{(0-t)}$  for estrone, a  $C_{max}$  for estrone, an  $AUC_{(0-t)}$  for total estrone, and a  $C_{max}$  for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an  $AUC_{(0-t)}$  for estradiol that is from 280.7467 pg·hr/ml to 438.6667 pg·hr/ml; a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml; an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg·hr/ml to 2842.5283 pg·hr/ml; a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml; an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng·hr/ml to 63.0476 ng·hr/ml; and a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

$AUC$ ,  $C_{max}$ , and  $T_{max}$  Parameters (D)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 1 mg and progesterone at a dosage of about 100 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation D in Table 4 above.

In some embodiments, administration of a composition comprising about 1 mg estradiol and about 100 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml; or
- (ii) a  $C_{max}$  for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml.

In some embodiments, administration of the composition to the subject produces both an  $AUC_{(0-t)}$  for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml, and a  $C_{max}$  for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:



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- (i) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (ii) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces both an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, and a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml;
- (ii) a  $C_{max}$  for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; or
- (iv) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml;
- (ii) a  $C_{max}$  for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; or
- (iii) a  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr.

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In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml;
- (ii) a  $C_{max}$  for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml; or
- (iii) a  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml, a mean  $C_{max}$  for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml, and a mean  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml, a mean  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml, and a mean  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml, a mean  $C_{max}$  for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml, and a mean  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml, a mean  $C_{max}$  for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml, and a mean  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, method of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 1 mg estradiol and about 100 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation D in Table 4 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an  $AUC_{(0-t)}$  for estradiol that is from 561.4933 pg·hr/ml to 877.3333 pg·hr/ml; a  $C_{max}$  for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; a  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr; an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; a  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr; an  $AUC_{(0-t)}$  for estrone that is from 3638.4363 pg·hr/ml to 5685.0567 pg·hr/ml; a  $C_{max}$  for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; a  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr; an  $AUC_{(0-t)}$  for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml; a  $C_{max}$  for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml; and a  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the

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pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation D in Table 4 above), and measuring one or more pharmacokinetic parameters selected from an  $AUC_{(0-t)}$  for estradiol, a  $C_{max}$  for estradiol, an  $AUC_{(0-t)}$  for progesterone, a  $C_{max}$  for progesterone, an  $AUC_{(0-t)}$  for estrone, a  $C_{max}$  for estrone, an  $AUC_{(0-t)}$  for total estrone, and a  $C_{max}$  for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an  $AUC_{(0-t)}$  for estradiol that is from 561.4933 pg-hr/ml to 877.3333 pg-hr/ml; a  $C_{max}$  for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml; an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng-hr/ml to 75.0543 ng-hr/ml; a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml; an  $AUC_{(0-t)}$  for estrone that is from 3638.4363 pg-hr/ml to 5685.0567 pg-hr/ml; a  $C_{max}$  for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml; an  $AUC_{(0-t)}$  for total estrone that is from 80.7010 ng-hr/ml to 126.0953 ng-hr/ml; and a  $C_{max}$  for total estrone that is from 14.1716 ng/ml to 22/1431 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

$AUC$ ,  $C_{max}$ , and  $T_{max}$  Parameters (E)

In some embodiments, a pharmaceutical composition of this disclosure comprises estradiol at a dosage of about 2 mg and progesterone at a dosage of about 200 mg. In some embodiments, the pharmaceutical composition comprises the formulation of Formulation E in Table 5 above.

In some embodiments, administration of a pharmaceutical composition comprising about 2 mg estradiol and about 200 mg progesterone to a subject produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml; or
- (ii) a  $C_{max}$  for estradiol that is from 52 pg/ml to 81 pg/ml.

In some embodiments, administration of the composition to the subject produces both an  $AUC_{(0-t)}$  for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml, and a  $C_{max}$  for estradiol that is from 52 pg/ml to 81 pg/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an  $AUC_{(0-t)}$  for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml; or
- (ii) a  $C_{max}$  for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject produces both an  $AUC_{(0-t)}$  for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml, and a  $C_{max}$  for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject produces, in a plasma sample from the subject,

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml;
- (ii) a  $C_{max}$  for estradiol that is from 52 pg/ml to 81 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml; or
- (iv) a  $C_{max}$  for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject further produces, in a plasma sample from the subject, a  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to the

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subject further produces, in a plasma sample from the subject, a  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr.

In some embodiments, administration of the pharmaceutical composition to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml;
- (ii) a  $C_{max}$  for estradiol that is from 52 pg/ml to 81 pg/ml;
- (iii) an  $AUC_{(0-t)}$  for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml; or
- (iv) a  $C_{max}$  for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the pharmaceutical composition to the subject produces both parameters (i) and (ii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the composition to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the composition to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the composition to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the composition to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the composition to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for estrone that is from 7277 pg-hr/ml to 11370 pg-hr/ml;
- (ii) a  $C_{max}$  for estrone that is from 341 pg/ml to 533 pg/ml; or
- (iii) a  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

- (i) an  $AUC_{(0-t)}$  for total estrone that is from 161 ng-h/ml to 252 ng-h/ml
- (ii) a  $C_{max}$  for total estrone that is from 28 ng/ml to 44 ng/ml; or
- (iii) a  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, a pharmaceutical composition comprising about 2 mg estradiol and about 200 mg progesterone is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., blood or plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml, a mean  $C_{max}$  for estradiol that is from 52 pg/ml to 81 pg/ml, and a mean  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml, a mean  $C_{max}$  for progesterone that is from 71 ng/ml

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to 112 ng/ml, and a mean  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for estrone that is from 7277 pg-hr/ml to 11370 pg-hr/ml, a mean  $C_{max}$  for estrone that is from 341 pg/ml to 533 pg/ml, and a mean  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean  $AUC_{(0-t)}$  for total estrone that is from 161 ng-h/ml to 252 ng-h/ml, a mean  $C_{max}$  for total estrone that is from 28 ng/ml to 44 ng/ml, and a mean  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, method of treating a subject with a pharmaceutical composition comprising estradiol and progesterone are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 2 mg estradiol and about 200 mg progesterone as described herein (e.g., a pharmaceutical composition having the formulation of Formulation E in Table 5 above), wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an  $AUC_{(0-t)}$  for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml; a  $C_{max}$  for estradiol that is from 52 pg/ml to 81 pg/ml; a  $T_{max}$  for estradiol that is from 7.2 hr to 11.3 hr; an  $AUC_{(0-t)}$  for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml; a  $C_{max}$  for progesterone that is from 71 ng/ml to 112 ng/ml; a  $T_{max}$  for progesterone that is from 2.4 hr to 3.8 hr; an  $AUC_{(0-t)}$  for estrone that is from 7277 pg-hr/ml to 11370 pg-hr/ml; a  $C_{max}$  for estrone that is from 341 pg/ml to 533 pg/ml; a  $T_{max}$  for estrone that is from 4.4 hr to 6.9 hr; an  $AUC_{(0-t)}$  for total estrone that is from 161 ng-h/ml to 252 ng-h/ml; a  $C_{max}$  for total estrone that is from 28 ng/ml to 44 ng/ml; and a  $T_{max}$  for total estrone that is from 2 hr to 3.1 hr.

In some embodiments, the method further comprises obtaining a sample from the subject (e.g., a blood or plasma sample) following administration of a single dose of the pharmaceutical composition (e.g., a pharmaceutical composition having the formulation of Formulation E in Table 5 above), and measuring one or more pharmacokinetic parameters selected from an  $AUC_{(0-t)}$  for estradiol, a  $C_{max}$  for estradiol, an  $AUC_{(0-t)}$  for progesterone, a  $C_{max}$  for progesterone, an  $AUC_{(0-t)}$  for estrone, a  $C_{max}$  for estrone, an  $AUC_{(0-t)}$  for total estrone, and a  $C_{max}$  for total estrone; wherein the presence of one or more of the following values is indicative of a therapeutically effective dose: an  $AUC_{(0-t)}$  for estradiol that is from 1123 pg-h/ml to 1755 pg-h/ml; a  $C_{max}$  for estradiol that is from 52 pg/ml to 81 pg/ml; an  $AUC_{(0-t)}$  for progesterone that is from 96 ng-hr/ml to 150 ng-hr/ml; a  $C_{max}$  for progesterone that is from 71 ng/ml to 112 ng/ml; an  $AUC_{(0-t)}$  for estrone that is from 7277 pg-hr/ml to 11370 pg-hr/ml; a  $C_{max}$  for estrone that is from 341 pg/ml to 533 pg/ml; an  $AUC_{(0-t)}$  for total estrone that is from 161 ng-h/ml to 252 ng-h/ml; and a  $C_{max}$  for total estrone that is from 28 ng/ml to 44 ng/ml. In some embodiments, the one or more pharmacokinetic parameters are measured about 18 hours, about 24 hours, about 18-36 hours, about 20-30 hours, about 22-26 hours, about 24-36 hours, about 36 hours, about 36-48 hours, about 40-48 hours, or about 48 hours after administration of the single dose.

In some embodiments, administration of the pharmaceutical composition as described herein results in the blood plasma estradiol concentration profile of FIG. 1. In some embodiments, administration of the pharmaceutical composition results in the blood plasma progesterone concentration profile of FIG. 2. In some embodiments, administration of

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the pharmaceutical composition results in the blood plasma estrone concentration profile of FIG. 3. In some embodiments, administration of the pharmaceutical composition results in the blood plasma total estrone concentration profile of FIG. 4.

#### Administration and Treatment

Pharmaceutical compositions comprising estradiol and progesterone as described herein (e.g., compositions comprising solubilized estradiol, suspended progesterone, and a medium chain solubilizing agent) can be prepared and administered in a wide variety of oral, parenteral and topical dosage forms. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Pharmaceutical compositions can be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, intrathecal, rectal, vaginal, sublingual or parenteral administration, including subcutaneous, intravenous, intramuscular, intrasternal, intracavernous, intrameatal, or intraurethral injection or infusion. In some embodiments, administration is by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally.

For preparing pharmaceutical compositions from the compounds of this disclosure, the pharmaceutically acceptable compositions can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid preparation can comprise one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Mack Publishing Co, Easton Pa. ("Remington's").

In general, the type of composition is selected based on the mode of administration. A pharmaceutical composition (e.g., for oral administration or delivery by injection) can be in the form of a liquid (e.g., an elixir, syrup, solution, emulsion or suspension). Alternatively, a pharmaceutical composition as described herein can take the form of a pill, tablet, or capsule containing the liquid oil, and thus, the composition can contain any of the following: a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose and derivatives thereof. The composition can also be formulated into a suppository disposed, for example, in a polyethylene glycol (PEG) solubilizing agent.

Administration of the compositions of this disclosure can be carried out via any of the accepted modes of administration. Thus, administration can be, for example, intravenous, topical, subcutaneous, transcutaneous, transdermal, intramuscular, oral, intra-joint, parenteral, intra-arteriole, intradermal, intraventricular, intracranial, intraperitoneal, intralesional, intranasal, rectal, vaginal, or by inhalation. In some embodiments, a composition as described herein is administered orally. For example, a pharmaceutical composition as described herein can be administered via capsules such as soft capsules.

In some embodiments, a pharmaceutical composition as described herein is administered once daily for a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100 days or more. In some embodiments, a pharmaceutical composition as

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described herein is administered daily for at least one week, at least two weeks, at least three weeks, at least four weeks, at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, at least twelve months, or more. In some embodiments, a pharmaceutical composition as described herein is administered as a continuous-combined therapy regimen.

In some embodiments, a 28-day or monthly regimen of daily doses is packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. In some embodiments, each daily dose contains both estradiol and progesterone. In some embodiments, one or more of the daily doses contains no estradiol or no progesterone. Daily doses that comprise no estradiol or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating the blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized or partially solubilized, or fully solubilized progesterone or solubilized estradiol in amounts as set forth herein, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of daily doses.

In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating conditions in subjects caused, at least in part, by estrogen deficiency, particularly for women with a uterus. For example, in embodiments, the pharmaceutical compositions disclosed herein are useful for the treatment of one or more of the following conditions: endometrial hyperplasia; secondary amenorrhea; prevention of preterm birth, when the subject has a shortened cervix; menopause-related symptoms including, for example, vasomotor symptoms; in relation to treatment of hypoestrogenism related symptoms including, for example and without limitation, hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes and vulvo-vaginal atrophy; and osteoporosis and other non-menopausal disease states or conditions treated with supplemental progesterone or estrogen. In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating vasomotor symptoms, including but not limited to, hot flashes and night sweats. In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating hot flashes and night sweats. In some embodiments, the pharmaceutical compositions disclosed herein are useful in treating hot flashes. Thus, in some embodiments, this disclosure provides methods of treating such a condition by administering to the subject a composition comprising estradiol and progesterone as described herein.

### III. EXAMPLES

The following examples are offered to illustrate, but not to limit, the claimed subject matter.

#### Example 1

In an exemplary embodiment, a soft gelatin capsule contains a pharmaceutical composition comprising suspended progesterone and solubilized estradiol:

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TABLE 6

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL® MCM, NF		82.57	577.97
GELUCIRE® 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

The encapsulated pharmaceutical composition of Table 6 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impeller, agitator, or other suitable means. Also for the purposes of this Example, heating or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas (N<sub>2</sub>). Mixing or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL® MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.±2° C. GELUCIRE® 44/14 may be added to the CAPMUL® MCM and mixed until dissolved (to increase the solubility of progesterone in the final solution, GELUCIRE® 44/14 was added at about 10% w/w). The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the GELUCIRE® 44/14 and the CAPMUL® MCM.

Heat may be removed from the GELUCIRE® 44/14 and CAPMUL® MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the GELUCIRE® 44/14, CAPMUL® MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

#### Example 2

An example of the final scale-up formulation is provided in Table 7. To manufacture, CAPMUL® MCM is heated to 40° C. GELUCIRE® 44/14 is heated to 65° C. and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until fully suspended.

TABLE 7

Quantitative Formula: Batch Size 10,000 capsules					
Item No.	Ingredient	Label Claim (mg)	% w/w	Qty/Capsule (mg)	Amount/Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL® MCM, NF		82.57	577.97	5.78
4.	GELUCIRE® 44/14, NF		10.0	70.00	0.70
Total:		100.00	700.00	7.00	



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## Example 3

In an exemplary embodiment, a soft gelatin capsule contains a pharmaceutical composition having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 8

Item No.	Ingredient	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL® MCM, NF		73.371	146.74	1467.42
4.	GELUCIRE® 44/14, NF		1.500	3.00	30.00
Total:		100.000	200.00 mg	2000.00	

To manufacture, CAPMUL® MCM is heated to 65° C. GELUCIRE® 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 4

In an exemplary embodiment, a soft gelatin capsule contains a pharmaceutical composition having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 9

Item No.	Ingredient	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7
3.	CAPMUL® MCM, NF		65.32	391.93	3919.3
4.	GELUCIRE® 44/14, NF		1.00	6.0	60.0
Total:		100.00	600.0 mg	6000.0	

To manufacture, CAPMUL® MCM is heated to 65° C. GELUCIRE® 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resulting pharmaceutical composition is encapsulated in soft gelatin capsules. Alternatively, GELUCIRE® 44/14 is heated to 65° C. and CAPMUL® MCM is heated to 40° C.±5° C. to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 40° C.; the mixture is then passed through a colloid mill one or more times, e.g., three times.

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## Example 5

Pharmacokinetics of the First Combination 17β-Estradiol/ Progesterone Capsule in Clinical Development for Hormone Therapy

The objective of this study was to evaluate the pharmacokinetic and oral bioavailability of a combination capsule of 17β-estradiol/progesterone in comparison to co-administration of the individual products ESTRACE® and PROMETRIUM®.

Subjects and Study Design:

An open label, balanced, randomized, single-dose, 2-treatment, 3-period, 3-sequence, crossover, partial-replicate, reference-scaled, oral, relative bioavailability study compared the bioavailability of an investigational 2-mg 17β-estradiol/200-mg progesterone combination capsule, without peanut oil (formulated in a manner similar to that set forth in Table 9), with that of co-administered 200-mg PROMETRIUM® (progesterone) and 2-mg ESTRACE® (17β-estradiol) tablets in healthy postmenopausal women aged 40-65 years (N=66). Key inclusion criteria for subjects included a BMI 18.50 to 29.99 kg/m<sup>2</sup> who were nonsmokers or ex-smokers (no smoking in the last 3 months). Key exclusion criteria for subjects included consuming grapefruit juice or poppy-containing foods within 48 hours before and throughout the study, use of any hormonal agent within 14 days before the study, and use of menopausal hormone therapy within 6 months before dosing.

Patients were randomly assigned sequentially to 1 of 3 dosing sequences of the same dose of the combination capsule (Test, T) and reference products (Reference, R): TRR, RTR, or RRT. 66 subjects were randomized and 62 (94.0%) completed the study. Subjects had a mean age of 49.5±5.6 years (range 40 to 64) and a mean BMI of 24.8±3.1 kg/m<sup>2</sup> (range 18.7-29.9).

After consuming a high-fat, high-calorie breakfast, each woman received a single dose of the combination (Test) capsule in 1 period of the study and single doses of the co-administered products (Reference) in each of the 2 remaining periods. Blood samples were collected within 75 minutes before dosing and post-dose at 0.25, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, and 48 hours after dosing to determine progesterone, free (un-conjugated) estradiol, and free and total (conjugated+free, including estrone sulfates) estrone concentrations. After collection of blood samples at each time point, the blood samples were centrifuged at 4000 RPM for 10 minutes at 4° C. to separate the plasma. The plasma from samples was separated into two aliquots. 1.5 mL from the plasma sample was transferred into aliquot I, and the remaining plasma sample was transferred into aliquot II. These aliquots were stored at -30° C. for interim storage, then at -70° C. until completion of the analysis.

Progesterone, estradiol, estrone, and total estrone in human plasma was determined using the LC-MS/MS method. The primary ( $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ ) and secondary ( $T_{max}$ ,  $t_{1/2}$ , and  $K_e$ ) PK parameters for each analyte were determined for each subject during each period by non-compartment analyses using baseline-adjusted concentrations. Statistical analyses were conducted using the SAS® statistical software.

Results: The mean, standard deviation (SD), geometric mean, coefficient of variation (CV %), minimum, median, and maximum were calculated for  $C_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $T_{max}$ ,  $t_{1/2}$ ,  $K_e$ ,  $K_{el\_lower}$ ,  $K_{el\_upper}$ , and  $AUC_{\%Extrap\_obs}$  for progesterone, estradiol, estrone, and total estrone. The results are presented in Tables 10, 11, 12, and 13 below. For each of Tables 10-13, "Test Product (T)" refers to the progesterone+estradiol pharmaceutical composition, while "Reference product (R1)" and "Reference product (R2)" refers to co-administered PROMETRIUM® (progesterone) and ESTRACE® (estradiol). Blood plasma concentrations of progesterone, estradiol, estrone, and total estrone over time are also shown in FIGS. 1-4.

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TABLE 10

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R <sub>1</sub> , R <sub>2</sub> ) for Progesterone						
Untransformed Data (Mean ± SD)						
PK Parameter	N	Test Product (T)	N	Reference product (R1)	N	Reference product (R2)
C <sub>max</sub> (ng/mL)	62	89.2222 ± 149.7309	62	72.7228 ± 101.8885	62	69.7590 ± 87.0777
AUC <sub>0-t</sub> (ng · hr/mL)	62	120.0869 ± 164.1385	62	125.9406 ± 152.3483	62	111.5867 ± 113.3200
AUC <sub>0-∞</sub> (ng · hr/mL)	57	131.3817 ± 172.4806	57	142.1332 ± 160.4853	56	126.6006 ± 117.2665
T <sub>max</sub> (hr)	62	3.00 (0.83-10.00)	62	3.00 (1.00-12.00)	62	4.00 (0.67-18.00)
K <sub>el</sub> (hr <sup>-1</sup> )	57	0.3064 ± 0.2427	57	0.2684 ± 0.1912	56	0.2795 ± 0.2475
t <sub>1/2</sub> (hr)	57	4.6445 ± 4.5366	57	5.1555 ± 4.9794	56	5.0389 ± 4.5887
K <sub>el_Lower</sub> (hr <sup>-1</sup> )	57	7.6667 ± 4.6047	57	7.4123 ± 4.2164	56	7.9018 ± 3.9120
K <sub>el_Upper</sub> (hr <sup>-1</sup> )	57	16.2218 ± 11.0051	57	19.1728 ± 12.3801	56	18.1975 ± 10.0858
AUC_Extra (%)	57	4.3374 ± 2.5528	57	4.8416 ± 3.7526	56	5.1868 ± 4.1434

\*Expressed in terms of median (range)

TABLE 11

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R <sub>1</sub> , R <sub>2</sub> ) for Estradiol			
Untransformed Data (Mean ± SD)			
PK Parameter	Test Product (T)	Reference product (R1)	Reference product (R2)
C <sub>max</sub> (pg/mL)	64.7902 ± 50.9833	69.1286 ± 33.0484	73.4236 ± 43.4077
AUC <sub>0-t</sub> (pg · hr/mL)	1403.7333 ± 763.8136	1508.2206 ± 876.7390	1658.2502 ± 976.5556
AUC <sub>0-∞</sub> (pg · hr/mL)	2459.4394 ± 4498.2737	2842.8805 ± 4582.6502	2110.9591 ± 1175.3995
T <sub>max</sub> (hr)	9.00(0.50-36.00)	10.0(0.50-35.12)	10.00(0.25-36.60)
K <sub>el</sub> (hr <sup>-1</sup> )	0.0438 ± 0.0197	0.0457 ± 0.0358	0.0464 ± 0.0338
t <sub>1/2</sub> (hr)	31.9104 ± 95.9769	25.0908 ± 28.8346	20.8774 ± 12.0825
K <sub>el_Lower</sub> (hr <sup>-1</sup> )	14.9472 ± 7.2715	14.9667 ± 7.0150	14.7953 ± 5.8774
K <sub>el_Upper</sub> (hr <sup>-1</sup> )	45.3602 ± 6.3668	44.3277 ± 7.4003	43.8330 ± 7.6449
AUC_Extra (%)	22.8106 ± 16.6498	25.4773 ± 20.2911	24.9566 ± 16.4713

\*Expressed in terms of median (range)

TABLE 12

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R <sub>1</sub> , R <sub>2</sub> ) for Free Estrone			
Untransformed Data (Mean ± SD)			
PK Parameter	Test Product (T)	Reference product (R1)	Reference product (R2)
C <sub>max</sub> (pg/mL)	426.5492 ± 179.3303	455.5107 ± 189.448	467.2302 ± 207.4373
AUC <sub>0-t</sub> (pg · hr/mL)	9096.0907 ± 4377.2730	10156.0282 ± 5140.5831	10507.3557 ± 5183.1289
AUC <sub>0-∞</sub> (pg · hr/mL)	11994.9695 ± 6678.5468	13445.9048 ± 8699.4068	14066.2362 ± 7563.2370
T <sub>max</sub> (hr)	5.50(0.83-36.00)	8.00(1.67-18.00)	10.00(1.67-18.00)
K <sub>el</sub> (hr <sup>-1</sup> )	0.0399 ± 0.0146	0.0424 ± 0.0172	0.0406 ± 0.0209
t <sub>1/2</sub> (hr)	20.3172 ± 9.4052	19.4595 ± 9.8711	20.7515 ± 9.3985
K <sub>el_Lower</sub> (hr <sup>-1</sup> )	13.8443 ± 7.0649	14.8871 ± 6.6459	14.9194 ± 6.4485
K <sub>el_Upper</sub> (hr <sup>-1</sup> )	46.0238 ± 5.5080	46.2547 ± 5.3060	46.2244 ± 5.3126
AUC_Extra (%)	21.2980 ± 11.2283	20.3648 ± 11.1060	21.8900 ± 11.8537

\*Expressed in terms of median (range)

TABLE 13

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R <sub>1</sub> , R <sub>2</sub> ) for Total Estrone						
Untransformed Data (Mean ± SD)						
PK Parameter	N	Test Product (T)	N	Reference product (R1)	N	Reference product (R2)
C <sub>max</sub> (ng/mL)	61	35.4289 ± 17.0856	61	19.8716 ± 7.4485	61	19.9048 ± 8.0288
AUC <sub>0-t</sub> (ng · hr/mL)	61	201.7524 ± 94.2081	61	182.7729 ± 88.8386	61	199.8295 ± 94.9392
AUC <sub>0-∞</sub> (ng · hr/mL)	61	213.2402 ± 104.6011	60	193.6387 ± 100.5831	56	203.0289 ± 81.4884
T <sub>max</sub> (hr)	61	2.50 (0.67-7.00)	61	4.00 (1.33-18.00)	61	4.00 (1.33-10.00)



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TABLE 13-continued

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R <sub>1</sub> , R <sub>2</sub> ) for Total Estrone						
Untransformed Data (Mean ± SD)						
PK Parameter	N	Test Product (T)	N	Reference product (R1)	N	Reference product (R2)
K <sub>el</sub> (hr <sup>-1</sup> )	61	0.0799 ± 0.0398	60	0.0803 ± 0.0399	56	0.0718 ± 0.0243
t <sub>1/2</sub> (hr)	61	10.3619 ± 4.0023	60	9.8448 ± 3.0702	56	10.7830 ± 3.6624
K <sub>el, Lower</sub> (hr <sup>-1</sup> )	61	13.0492 ± 6.8585	60	13.5945 ± 8.0129	56	11.8870 ± 6.8696
K <sub>el, Upper</sub> (hr <sup>-1</sup> )	61	45.3979 ± 6.6589	60	46.3775 ± 5.2525	56	46.7054 ± 4.3888
AUC <sub>Extra</sub> (%)	61	4.5030 ± 3.7366	60	4.5913 ± 3.4953	56	5.3450 ± 3.9831

\*Expressed in terms of median (range)

## Example 6

Pharmacokinetic data (C<sub>max</sub>, AUC<sub>(0-t)</sub>, AUC<sub>(0-∞)</sub>, and T<sub>max</sub>) for progesterone, estradiol, free estrone, and total estrone is presented in Tables 14-17. Pharmaceutical compositions A-E are disclosed in Tables 1-5. The pK values for pharmaceutical composition E were calculated as disclosed in Example 5. For pharmaceutical compositions A-D, expected pharmacokinetic data is calculated from the data disclosed for pharmaceutical composition E.

TABLE 14

Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Progesterone						
Pharmaceutical Composition	Progesterone Content	Estradiol Content	C <sub>max</sub> (ng/mL)	AUC <sub>(0-t)</sub> (ng · hr/mL)	AUC <sub>(0-∞)</sub> (ng · hr/mL)	T <sub>max</sub> (hr)
A	50 mg	0.25 mg	22.30555	30.0217	32.8454	3.00
B	50 mg	0.50 mg	22.3055	30.0217	32.8454	3.00
C	100 mg	0.50 mg	44.6111	60.0435	65.6909	3.00
D	100 mg	1 mg	44.6111	60.0435	65.6909	3.00
E	200 mg	2 mg	89.2222	120.0869	131.3817	3.00

TABLE 15

Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Estradiol						
Pharmaceutical Composition	Progesterone Content	Estradiol Content	C <sub>max</sub> (pg/mL)	AUC <sub>(0-t)</sub> (pg · hr/mL)	AUC <sub>(0-∞)</sub> (pg · hr/mL)	T <sub>max</sub> (hr)
A	50 mg	0.25 mg	8.0988	175.4667	307.4299	9.00
B	50 mg	0.50 mg	16.1976	350.9333	614.8599	9.00
C	100 mg	0.50 mg	16.1976	350.9333	614.8599	9.00
D	100 mg	1 mg	32.3951	701.8667	1229.7197	9.00
E	200 mg	2 mg	64.7902	1403.7333	2459.4394	9.00

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TABLE 16

Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Free Estrone						
Pharmaceutical Composition	Progesterone Content	Estradiol Content	C <sub>max</sub> (pg/mL)	AUC <sub>(0-t)</sub> (pg · hr/mL)	AUC <sub>(0-∞)</sub> (pg · hr/mL)	T <sub>max</sub> (hr)
A	50 mg	0.25 mg	53.3187	1137.0113	1499.3712	5.50
B	50 mg	0.50 mg	106.6373	2274.0227	2998.7424	5.50
C	100 mg	0.50 mg	106.6373	2274.0227	2998.7424	5.50
D	100 mg	1 mg	213.2746	4548.0454	5997.4848	5.50
E	200 mg	2 mg	426.5492	9096.0907	11994.9695	5.50

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TABLE 17

Summary of Pharmacokinetic Parameters of the Pharmaceutical Compositions of Tables 1-5 for Total Estrone						
Pharmaceutical Composition	Progesterone Content	Estradiol Content	C <sub>max</sub> (ng/mL)	AUC <sub>(0-t)</sub> (ng · hr/mL)	AUC <sub>(0-∞)</sub> (ng · hr/mL)	T <sub>max</sub> (hr)
A	50 mg	0.25 mg	4.4286	25.2191	26.6550	2.50
B	50 mg	0.50 mg	8.8572	50.4381	53.3101	2.50
C	100 mg	0.50 mg	8.8572	50.4381	53.3101	2.50
D	100 mg	1 mg	17.7145	100.8762	106.6201	2.50
E	200 mg	2 mg	35.4289	201.7524	213.2402	2.50

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The ranges of expected pK values for each of the pharmaceutical compositions of Tables 1-4 are disclosed in Tables 18-21, respectively.

TABLE 18

pK Ranges for the Pharmaceutical Composition of Table 1 (Pharmaceutical Composition A)			
	C <sub>max</sub>	AUC <sub>(0-t)</sub>	AUC <sub>(0-∞)</sub>
Progesterone	17.8444 ng/mL to 27.8819 ng/mL	24.0174 ng · hr/mL to 37.5272 ng · hr/mL	26.2763 ng · hr/mL to 41.0568 ng · hr/mL
Estradiol	6.4790 pg/mL to 10.1235 pg/mL	140.3733 pg · hr/mL to 219.3333 pg · hr/mL	245.9439 pg · hr/mL to 384.2874 pg · hr/mL
Free estrone	42.6549 pg/mL to 66.6483 pg/mL	909.6091 pg · hr/mL to 1421.2642 pg · hr/mL	1199.4970 pg · hr/mL to 1874.2140 pg · hr/mL

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TABLE 18-continued

pK Ranges for the Pharmaceutical Composition of Table 1 (Pharmaceutical Composition A)			
	$C_{max}$	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Total estrone	3.5429 ng/mL to 5.5358 ng/mL	20.1752 ng · hr/mL to 31.5238 ng · hr/mL	21.3240 ng · hr/mL to 33.3188 ng · hr/mL

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TABLE 19

pK Ranges for the Pharmaceutical Composition of Table 2 (Pharmaceutical Composition B)			
	$C_{max}$	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Progesterone	17.8444 ng/mL to 27.8819 ng/mL	24.0174 ng · hr/mL to 37.5272 ng · hr/mL	26.2763 ng · hr/mL to 41.0568 ng · hr/mL
Estradiol	12.9580 pg/mL to 20.2469 pg/mL	280.7467 pg · hr/mL to 438.6667 pg · hr/mL	491.8879 pg · hr/mL to 768.5748 pg · hr/mL
Free estrone	85.3098 pg/mL to 133.2966 pg/mL	1819.2181 pg · hr/mL to 2842.5283 pg · hr/mL	2398.9939 pg · hr/mL to 3748.4280 pg · hr/mL
Total estrone	7.0858 ng/mL to 11.0715 ng/mL	40.3505 ng · hr/mL to 63.0476 ng · hr/mL	42.6480 ng · hr/mL to 66.6376 ng · hr/mL

TABLE 20

pK Ranges for the Pharmaceutical Composition of Table 3 (Pharmaceutical Composition C)			
	$C_{max}$	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Progesterone	35.6889 ng/mL to 55.7639 ng/mL	48.0348 ng · hr/mL to 75.0543 ng · hr/mL	52.5527 ng · hr/mL to 82.1136 ng · hr/mL
Estradiol	12.9580 pg/mL to 20.2469 pg/mL	280.7467 pg · hr/mL to 438.6667 pg · hr/mL	491.8879 pg · hr/mL to 768.5748 pg · hr/mL
Free estrone	85.3098 pg/mL to 133.2966 pg/mL	1819.2181 pg · hr/mL to 2842.5283 pg · hr/mL	2398.9939 pg · hr/mL to 3748.4280 pg · hr/mL
Total estrone	7.0858 ng/mL to 11.0715 ng/mL	40.3505 ng · hr/mL to 63.0476 ng · hr/mL	42.6480 ng · hr/mL to 66.6376 ng · hr/mL

TABLE 21

pK Ranges for the Pharmaceutical Composition of Table 4 (Pharmaceutical Composition D)			
	$C_{max}$	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Progesterone	35.6889 ng/mL to 55.7639 ng/mL	48.0348 ng · hr/mL to 75.0543 ng · hr/mL	52.5527 ng · hr/mL to 82.1136 ng · hr/mL
Estradiol	25.9161 pg/mL to 40.4939 pg/mL	561.4933 pg · hr/mL to 877.3333 pg · hr/mL	983.7758 pg · hr/mL to 1537.1496 pg · hr/mL
Free estrone	170.6197 pg/mL to 266.5933 pg/mL	3638.4363 pg · hr/mL to 5685.0567 pg · hr/mL	4797.9878 pg · hr/mL to 7496.8559 pg · hr/mL
Total estrone	14.1716 ng/mL to 22.1431 ng/mL	80.7010 ng · hr/mL to 126.0953 ng · hr/mL	85.2961 ng · hr/mL to 133.2751 ng · hr/mL

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various

alternatives together with details of the structure and function of the devices or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the

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appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

What is claimed is:

1. A method of treating a subject having vasomotor symptoms associated with estrogen deficiency, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising:

about 0.25 mg estradiol, wherein at least 80% of the estradiol in the composition is solubilized estradiol; progesterone, wherein the progesterone comprises suspended progesterone; and

a medium-chain oil comprising medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids, and wherein the entire amount of the estradiol and the progesterone in the composition is present in the oil;

wherein administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an area under the curve  $(AUC)_{(0-t)}$  for estradiol that is from 140.3733 pg-hr/ml to 219.3333 pg-hr/ml; and  
(ii) a  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

2. The method of claim 1, wherein the subject is female.

3. The method of claim 1, wherein the subject is a woman having a uterus.

4. The method of claim 1, wherein administration of the composition to the subject produces both an  $AUC_{(0-t)}$  for estradiol that is from 140.3733 pg-hr/ml to 219.3333 pg-hr/ml and a  $C_{max}$  for estradiol that is from 6.4790 pg/ml to 10.1235 pg/ml.

5. The method of claim 1, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng-hr/ml to 37.5272 ng-hr/ml; and  
(ii) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

6. The method of claim 1, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an  $AUC_{(0-t)}$  for estrone that is from 909.6091 pg-hr/ml to 1421.2642 pg-hr/ml; and  
(ii) a  $C_{max}$  for estrone that is from 42.6549 pg/ml to 66.6483 pg/ml.

7. The method of claim 1, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an  $AUC_{(0-t)}$  for total estrone that is from 20.1752 ng-hr/ml to 31.5238 ng-hr/ml; and  
(ii) a  $C_{max}$  for total estrone that is from 3.5429 ng/ml to 5.5358 ng/ml.

8. A method of treating a subject having vasomotor symptoms associated with estrogen deficiency, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising:

about 0.5 mg estradiol, wherein at least 80% of the estradiol in the composition is solubilized estradiol; progesterone, wherein the progesterone comprises suspended progesterone; and

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a medium-chain oil comprising medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids, and wherein the entire amount of the estradiol and the progesterone in the composition is present in the oil;

wherein administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an area under the curve  $(AUC)_{(0-t)}$  for estradiol that is from 280.7467 pg-hr/ml to 438.6667 pg-hr/ml; and  
(ii) a  $C_{max}$  for estradiol that is from 12.9580 pg/ml to 20.2469 pg/ml.

9. The method of claim 8, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an  $AUC_{(0-t)}$  for estrone that is from 1819.2181 pg-hr/ml to 2842.5283 pg-hr/ml; and  
(ii) a  $C_{max}$  for estrone that is from 85.3098 pg/ml to 133.2966 pg/ml.

10. The method of claim 8, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an  $AUC_{(0-t)}$  for total estrone that is from 40.3505 ng-hr/ml to 63.0476 ng-hr/ml; and  
(ii) a  $C_{max}$  for total estrone that is from 7.0858 ng/ml to 11.0715 ng/ml.

11. The method of claim 8, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng-hr/ml to 75.0543 ng-hr/ml; and  
(ii) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

12. A method of treating a subject having vasomotor symptoms associated with estrogen deficiency, the method comprising administering to the subject an effective amount of a pharmaceutical composition comprising:

about 1 mg estradiol, wherein at least 80% of the estradiol in the composition is solubilized estradiol; progesterone, wherein the progesterone comprises suspended progesterone; and

a medium-chain (C6-C12) oil comprising medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acid esters are predominantly esters of C6 to C12 fatty acids, and wherein the entire amount of the estradiol and the progesterone in the composition is present in the oil;

wherein administration of the composition to the subject produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an area under the curve  $(AUC)_{(0-t)}$  for estradiol that is from 561.4933 pg-hr/ml to 877.3333 pg-hr/ml; and  
(ii) a  $C_{max}$  for estradiol that is from 25.9161 pg/ml to 40.4939 pg/ml.

13. The method of claim 12, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

(i) an  $AUC_{(0-t)}$  for estrone that is from 3638.4363 pg-hr/ml to 5685.0567 pg-hr/ml; and

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- (i) a  $C_{max}$  for estrone that is from 170.6197 pg/ml to 266.5933 pg/ml.

14. The method of claim 12, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an  $AUC_{(0-t)}$  for total estrone that is from 80.7010 ng·hr/ml to 126.0953 ng·hr/ml; and  
 (ii) a  $C_{max}$  for total estrone that is from 14.1716 ng/ml to 22.1431 ng/ml.

15. The method of claim 8, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an  $AUC_{(0-t)}$  for progesterone that is from 24.0174 ng·hr/ml to 37.5272 ng·hr/ml; and  
 (ii) a  $C_{max}$  for progesterone that is from 17.8444 ng/ml to 27.8819 ng/ml.

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16. The method of claim 12, wherein administration of the composition to the subject further produces, in a plasma sample from the subject, one or both parameters selected from:

- (i) an  $AUC_{(0-t)}$  for progesterone that is from 48.0348 ng·hr/ml to 75.0543 ng·hr/ml; and  
 (ii) a  $C_{max}$  for progesterone that is from 35.6889 ng/ml to 55.7639 ng/ml.

17. The method of claim 1, wherein the composition comprises about 0.25 mg estradiol and about 50 mg progesterone.

18. The method of claim 8, wherein the composition comprises about 0.5 mg estradiol and about 50 mg progesterone.

19. The method of claim 8, wherein the composition comprises about 0.5 mg estradiol and about 100 mg progesterone.

20. The method of claim 12, wherein the composition comprises about 1 mg estradiol and about 100 mg progesterone.

\* \* \* \* \*

# EXHIBIT M





US010639375B2

(12) **United States Patent**  
**Bernick et al.**

(10) **Patent No.:** **US 10,639,375 B2**

(45) **Date of Patent:** **\*May 5, 2020**

(54) **PROGESTERONE FORMULATIONS**

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(2013.01)

(58) **Field of Classification Search**

CPC ..... A51K 31/57; A51K 31/565; A61K 47/10;

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See application file for complete search history.

(56) **References Cited**

**U.S. PATENT DOCUMENTS**

1,967,351 A	7/1934	Dolay
2,232,438 A	2/1941	Butenandt
2,379,832 A	7/1945	Serini et al.
2,649,399 A	8/1953	Beall et al.
3,198,707 A	8/1965	Nomine et al.
3,478,070 A	11/1969	Stein et al.
3,526,648 A	9/1970	Bertin et al.
3,710,795 A	1/1973	Higuchi et al.
3,729,560 A	4/1973	Hagerman
3,729,566 A	4/1973	Ericsson et al.
3,755,573 A	8/1973	Berman
3,755,575 A	8/1973	Lerner
3,903,880 A	9/1975	Higuchi et al.
3,916,898 A	11/1975	Robinson
3,916,899 A	11/1975	Theeuwes et al.
3,921,636 A	11/1975	Zaffaroni
3,923,997 A	12/1975	Meuly
3,948,254 A	4/1976	Zaffaroni
3,971,367 A	7/1976	Zaffaroni
3,977,404 A	8/1976	Theeuwes
3,993,072 A	11/1976	Zaffaroni
4,008,719 A	2/1977	Theeuwes et al.
4,012,496 A	3/1977	Schopflin et al.
4,014,334 A	3/1977	Theeuwes et al.
4,014,987 A	3/1977	Heller et al.
4,016,251 A	4/1977	Higuchi et al.
4,071,623 A	1/1978	van der Vies

(Continued)

**FOREIGN PATENT DOCUMENTS**

BR	P1 1001367-9 A2	7/2012
CA	2548281 A1	6/2005

(Continued)

**OTHER PUBLICATIONS**

US 6,214,374 B1, 04/2001, Schmirler et al. (withdrawn)

(Continued)

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(57) **ABSTRACT**

Various pharmaceutical formulations are disclosed herein. For example, a pharmaceutical formulation is disclosed comprising ultra-micronized progesterone.

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

4,093,709	A	6/1978	Choi et al.	5,653,983	A	8/1997	Meybeck et al.
4,154,820	A	5/1979	Simoons	5,656,286	A	8/1997	Miranda et al.
4,155,991	A	5/1979	Schopflin et al.	5,660,839	A	8/1997	Allec et al.
4,196,188	A	4/1980	Besins	5,662,927	A	9/1997	Ehrlich et al.
4,215,691	A	8/1980	Wong	5,663,160	A	9/1997	Meybeck et al.
4,237,885	A	12/1980	Wong et al.	5,676,968	A	10/1997	Lipp et al.
4,310,510	A	1/1982	Sherman et al.	5,677,292	A	10/1997	Li et al.
4,327,725	A	5/1982	Cortese et al.	5,686,097	A	11/1997	Taskovich et al.
4,372,951	A	2/1983	Vorys	5,693,335	A	12/1997	Xia et al.
4,384,096	A	5/1983	Sonnabend	5,694,947	A	12/1997	Lehtinen et al.
4,393,871	A	7/1983	Vorhauer et al.	5,700,480	A	12/1997	Hille et al.
4,402,695	A	9/1983	Wong	5,709,844	A	1/1998	Arbeit et al.
4,423,151	A	12/1983	Baranczuk	5,719,197	A	2/1998	Kanios et al.
4,449,980	A	5/1984	Millar et al.	5,735,801	A	4/1998	Caillouetie
4,610,687	A	9/1986	Fogwell	5,739,176	A	4/1998	Dunn et al.
4,629,449	A	12/1986	Wong	5,744,463	A	4/1998	Bair
4,732,763	A	3/1988	Beck et al.	5,747,058	A	5/1998	Tipton
4,738,957	A	4/1988	Laurent et al.	5,762,614	A	6/1998	Caillouette
4,756,907	A	7/1988	Beck et al.	5,770,176	A	6/1998	Nargessi
4,762,717	A	8/1988	Crowley, Jr.	5,770,219	A	6/1998	Chiang
4,788,062	A	11/1988	Gale et al.	5,770,220	A	6/1998	Meconi et al.
4,816,257	A	3/1989	Buster et al.	5,770,227	A	6/1998	Dong et al.
4,822,616	A	4/1989	Zimmermann et al.	5,776,495	A	7/1998	Duclos et al.
4,865,848	A	9/1989	Cheng et al.	5,780,044	A	7/1998	Yewey et al.
4,900,734	A	2/1990	Maxson et al.	5,780,050	A	7/1998	Jain et al.
4,906,475	A	3/1990	Kim	5,788,980	A	8/1998	Nabahi
4,942,158	A	7/1990	Sarpotdar et al.	5,788,984	A	8/1998	Guenther et al.
4,961,931	A	10/1990	Wong	5,789,442	A	8/1998	Garfield et al.
5,030,629	A	7/1991	Rajadhyaksha	5,811,416	A	9/1998	Chwalisz et al.
5,064,654	A	11/1991	Berner et al.	5,811,547	A	9/1998	Nakamichi et al.
5,108,995	A	4/1992	Casper	5,814,329	A	9/1998	Shah
5,128,138	A	7/1992	Blank	5,820,878	A	10/1998	Hirano et al.
5,130,137	A	7/1992	Crowley, Jr.	5,827,200	A	10/1998	Caillouetie
5,140,021	A	8/1992	Maxson et al.	5,840,327	A	11/1998	Gale et al.
5,211,952	A	5/1993	Spicer et al.	5,843,468	A	12/1998	Burkoth et al.
5,252,334	A	10/1993	Chiang et al.	5,843,979	A	12/1998	Wille et al.
5,280,023	A	1/1994	Ehrlich et al.	5,858,394	A	1/1999	Lipp et al.
5,288,496	A	2/1994	Lewis	5,863,552	A	1/1999	Yue
5,340,584	A	8/1994	Spicer et al.	5,866,603	A	2/1999	Li et al.
5,340,585	A	8/1994	Pike et al.	5,882,676	A	3/1999	Lee et al.
5,340,586	A	8/1994	Pike et al.	5,885,612	A	3/1999	Meconi et al.
5,362,497	A	11/1994	Yamada et al.	5,888,533	A	3/1999	Dunn
5,382,573	A	1/1995	Casper	5,891,462	A	4/1999	Carrara
5,393,528	A	2/1995	Staab	5,891,868	A	4/1999	Cummings et al.
5,393,529	A	2/1995	Hoffmann et al.	5,898,038	A	4/1999	Yallampalli et al.
5,419,910	A	5/1995	Lewis	5,902,603	A	5/1999	Chen et al.
5,468,736	A	11/1995	Hodgen	5,904,931	A	5/1999	Lipp et al.
5,474,783	A	12/1995	Miranda et al.	5,906,830	A	5/1999	Farinas et al.
5,480,776	A	1/1996	Dullien	5,912,010	A	6/1999	Wille et al.
5,514,673	A	5/1996	Heckenmueller et al.	5,916,176	A	6/1999	Caillouetie
5,516,528	A	5/1996	Hughes et al.	RE36,247	E	7/1999	Plunkett et al.
5,527,534	A	6/1996	Myhling	5,919,477	A	7/1999	Bevan et al.
5,529,782	A	6/1996	Staab	5,922,349	A	7/1999	Elliesen et al.
5,538,736	A	7/1996	Hoffmann et al.	5,928,666	A	7/1999	Farinas et al.
5,543,150	A	8/1996	Bologna et al.	5,942,243	A	8/1999	Shah
5,547,948	A	8/1996	Barcomb	5,952,000	A	9/1999	Venkateshwaran et al.
5,556,635	A	9/1996	Istin et al.	5,958,446	A	9/1999	Miranda et al.
5,565,199	A	10/1996	Page et al.	5,962,445	A	10/1999	Stewart
5,567,831	A	10/1996	Li	5,968,919	A	10/1999	Samour et al.
5,569,652	A	10/1996	Beier et al.	5,972,372	A	10/1999	Saleh et al.
5,580,572	A	12/1996	Mikler et al.	5,985,311	A	11/1999	Cordes et al.
5,582,592	A	12/1996	Kendrick	5,985,850	A	11/1999	Falk et al.
5,585,370	A	12/1996	Casper	5,985,861	A	11/1999	Levine et al.
5,595,759	A	1/1997	Wright et al.	5,989,568	A	11/1999	Breton et al.
5,595,970	A	1/1997	Garfield et al.	5,993,856	A	11/1999	Ragavan et al.
5,605,702	A	2/1997	Teillaud et al.	6,001,846	A	12/1999	Edwards et al.
5,607,691	A	3/1997	Hale et al.	6,007,835	A	12/1999	Bon-Lapillonne et al.
5,607,693	A	3/1997	Bonte et al.	6,010,715	A	1/2000	Wick et al.
5,609,617	A	3/1997	Shealy et al.	6,013,276	A	1/2000	Math et al.
5,620,705	A	4/1997	Dong et al.	6,022,562	A	2/2000	Autant et al.
5,626,866	A	5/1997	Ebert et al.	6,024,974	A	2/2000	Li
5,629,021	A	5/1997	Wright	6,024,976	A	2/2000	Miranda et al.
5,633,011	A	5/1997	Dong et al.	6,028,057	A	2/2000	Burns
5,633,242	A	5/1997	Oettel	6,030,948	A	2/2000	Mann
5,639,743	A	6/1997	Kaswan et al.	6,039,968	A	3/2000	Nabahi
				6,040,340	A	3/2000	Chwalisz et al.
				6,056,972	A	5/2000	Hermesmeier
				6,060,077	A	5/2000	Meignant
				6,068,853	A	5/2000	Giannos et al.

## US 10,639,375 B2

Page 3

(56)

## References Cited

## U.S. PATENT DOCUMENTS

6,074,625	A	6/2000	Hawthorne et al.	6,468,526	B2	10/2002	Chrisope
6,077,531	A	6/2000	Salin-Drouin	6,469,016	B1	10/2002	Place et al.
6,080,118	A	6/2000	Blythe	6,472,434	B1	10/2002	Place et al.
6,083,178	A	7/2000	Caillouetie	6,479,232	B1	11/2002	Howett et al.
6,086,916	A	7/2000	Agnus et al.	6,495,160	B2	12/2002	Esposito et al.
6,087,352	A	7/2000	Trout	6,500,814	B1	12/2002	Hesch
6,090,404	A	7/2000	Meconi et al.	6,503,896	B1	1/2003	Tanabe et al.
6,096,338	A	8/2000	Lacy et al.	6,511,969	B1	1/2003	Hermismeyer
6,106,848	A	8/2000	Preuilh et al.	6,521,250	B2	2/2003	Meconi et al.
6,117,446	A	9/2000	Place	6,526,980	B1	3/2003	Tracy et al.
6,117,450	A	9/2000	Dittgen et al.	6,528,094	B1	3/2003	Savoir et al.
6,124,362	A	9/2000	Bradbury et al.	6,531,149	B1	3/2003	Kirstgen et al.
6,133,251	A	10/2000	Dittgen et al.	6,537,580	B1	3/2003	Savoir et al.
6,133,320	A	10/2000	Yallampalli et al.	6,538,039	B2	3/2003	Laurent
6,139,868	A	10/2000	Hoffmann	6,544,196	B2	4/2003	Caillouette
6,139,873	A	10/2000	Hughes, Jr. et al.	6,544,553	B1	4/2003	Hsia et al.
6,149,935	A	11/2000	Chiang et al.	6,548,053	B1	4/2003	Stewart et al.
6,153,216	A	11/2000	Cordes et al.	6,548,491	B2	4/2003	Tanabe et al.
6,165,491	A	12/2000	Grasset et al.	6,551,611	B2	4/2003	Elliesen et al.
6,165,975	A	12/2000	Adams et al.	6,555,131	B1	4/2003	Wolff et al.
6,187,323	B1	2/2001	Aiache et al.	6,562,367	B1	5/2003	Wolff et al.
6,187,339	B1	2/2001	de Haan et al.	6,562,370	B2	5/2003	Luo et al.
6,190,331	B1	2/2001	Caillouetie	6,562,790	B2	5/2003	Chein et al.
6,201,072	B1	3/2001	Rathi et al.	6,569,463	B2	5/2003	Patel et al.
6,217,886	B1	4/2001	Önyüksel et al.	6,583,129	B1	6/2003	Mazer et al.
6,225,297	B1	5/2001	Stockemann et al.	6,586,006	B2	7/2003	Roser et al.
6,227,202	B1	5/2001	Matapurkar	6,589,549	B2	7/2003	Shin et al.
6,228,383	B1	5/2001	Hansen et al.	6,593,317	B1	7/2003	de Ziegler et al.
6,228,852	B1	5/2001	Shaak	6,599,519	B1	7/2003	Seo et al.
6,242,509	B1	6/2001	Berger et al.	6,610,652	B2	8/2003	Adams et al.
6,245,811	B1	6/2001	Horrobin et al.	6,610,670	B2	8/2003	Backensfeld et al.
6,262,115	B1	7/2001	Guittard et al.	6,610,674	B1	8/2003	Schreiber
6,264,980	B1	7/2001	Hille	6,635,274	B1	10/2003	Masiz et al.
6,267,984	B1	7/2001	Beste et al.	6,638,528	B1	10/2003	Kanios
6,274,165	B1	8/2001	Meconi et al.	6,638,536	B2	10/2003	Savoir et al.
6,277,418	B1	8/2001	Marakverich et al.	6,645,528	B1	11/2003	Straub et al.
6,283,927	B1	9/2001	Caillouetie	6,649,155	B1	11/2003	Dunlop et al.
6,287,588	B1	9/2001	Shih et al.	6,653,298	B2	11/2003	Potter et al.
6,287,693	B1	9/2001	Savoir et al.	6,656,929	B1	12/2003	Agnus et al.
6,294,188	B1	9/2001	Raga Van et al.	6,660,726	B2	12/2003	Hill et al.
6,294,192	B1	9/2001	Patel et al.	6,663,608	B2	12/2003	Rathbone et al.
6,294,550	B1	9/2001	Place et al.	6,663,895	B2	12/2003	Savoir et al.
6,299,900	B1	10/2001	Reed et al.	6,682,757	B1	1/2004	Wright
6,303,132	B1	10/2001	Nelson	6,692,763	B1	2/2004	Cummings et al.
6,303,588	B1	10/2001	Danielov	6,708,822	B1	3/2004	Muni
6,306,841	B1	10/2001	Place et al.	6,720,001	B2	4/2004	Chen et al.
6,306,914	B1	10/2001	de Ziegler et al.	6,737,081	B2	5/2004	Savoir et al.
6,309,669	B1	10/2001	Setterstrom et al.	6,740,333	B2	5/2004	Becket et al.
6,309,848	B1	10/2001	Howett et al.	6,743,448	B2	6/2004	Kryger
6,312,703	B1	11/2001	Orthofer	6,743,815	B2	6/2004	Huebner et al.
6,328,987	B1	12/2001	Marini	6,747,018	B2	6/2004	Tanabe et al.
6,342,491	B1	1/2002	Dey et al.	6,750,291	B2	6/2004	Kim et al.
6,344,211	B1	2/2002	Hille	6,756,208	B2	6/2004	Griffin et al.
6,372,209	B1	4/2002	Chrisope	6,776,164	B2	8/2004	Bunt et al.
6,372,245	B1	4/2002	Bowman et al.	6,787,152	B2	9/2004	Kirby et al.
6,372,246	B1	4/2002	Wei et al.	6,805,877	B2	10/2004	Massara et al.
6,387,390	B1	5/2002	Deaver et al.	6,809,085	B1	10/2004	Elson et al.
6,402,705	B1	6/2002	Caillouette	6,818,226	B2	11/2004	Reed et al.
6,416,778	B1	7/2002	Raga Van et al.	6,821,524	B2	11/2004	Marini
6,420,352	B1	7/2002	Knowles	6,841,716	B1	1/2005	Tsutsumi
6,423,039	B1	7/2002	Rathbone et al.	6,844,334	B2	1/2005	Hill et al.
6,423,683	B1	7/2002	Heaton et al.	6,855,703	B1	2/2005	Hill et al.
6,432,438	B1	8/2002	Shukla	6,860,859	B2	3/2005	Mehrotra et al.
6,436,633	B1	8/2002	Kreider et al.	6,866,865	B2	3/2005	Hsia et al.
6,440,454	B1	8/2002	Santoro et al.	6,869,969	B2	3/2005	Heubner et al.
6,444,224	B1	9/2002	Rathbone et al.	6,878,518	B2	4/2005	Whitehead
6,444,234	B1	9/2002	Kirby et al.	6,901,278	B1	5/2005	Notelovitz
6,451,300	B1	9/2002	Dunlop et al.	6,905,705	B2	6/2005	Palm et al.
6,451,339	B2	9/2002	Patel et al.	6,911,211	B2	6/2005	Eini et al.
6,451,779	B1	9/2002	Hesch	6,911,438	B2	6/2005	Wright
6,455,246	B1	9/2002	Howett et al.	6,923,988	B2	8/2005	Patel et al.
6,455,517	B1	9/2002	Tanabe et al.	6,924,274	B2	8/2005	Lardy et al.
6,465,004	B1	10/2002	Rossi-Montero et al.	6,932,983	B1	8/2005	Straub et al.
6,465,005	B1	10/2002	Biali et al.	6,939,558	B2	9/2005	Massara et al.
6,465,006	B1	10/2002	Zhang et al.	6,943,021	B2	9/2005	Klausner et al.
				6,958,327	B1	10/2005	Hillisch et al.
				6,960,337	B2	11/2005	Daniels et al.
				6,962,691	B1	11/2005	Lulla et al.
				6,962,908	B2	11/2005	Aloba et al.

## US 10,639,375 B2

Page 4

(56)

## References Cited

## U.S. PATENT DOCUMENTS

6,967,194 B1	11/2005	Matsuo et al.	7,829,115 B2	11/2010	Besins et al.
6,974,569 B2	12/2005	Dunlop et al.	7,829,116 B2	11/2010	Griswold et al.
6,977,250 B2	12/2005	Rodriguez	RE42,012 E	12/2010	Deaver et al.
6,978,945 B2	12/2005	Wong	7,850,992 B2	12/2010	Kim et al.
6,995,149 B1	2/2006	Endrikat et al.	7,854,753 B2	12/2010	Kraft et al.
7,004,321 B1	2/2006	Palm et al.	7,858,607 B2	12/2010	Mamchur
7,005,429 B2	2/2006	Dey et al.	RE42,072 E	1/2011	Deaver et al.
7,011,846 B2	3/2006	Shojaei et al.	7,862,552 B2	1/2011	Mcintyre et al.
7,018,992 B2	3/2006	Koch et al.	7,867,990 B2	1/2011	Schultz et al.
7,030,104 B2	4/2006	Gray et al.	7,871,643 B2	1/2011	Lizio et al.
7,030,157 B2	4/2006	Ke et al.	7,879,830 B2	2/2011	Wiley
RE39,104 E	5/2006	Duclos et al.	7,884,093 B2	2/2011	Creasy et al.
7,074,779 B2	7/2006	Sui et al.	7,925,519 B2	4/2011	Greene
7,083,590 B1	8/2006	Bunt et al.	7,939,104 B2	5/2011	Barbera et al.
7,091,213 B2	8/2006	Metcalfe, III et al.	7,943,602 B2	5/2011	Bunschoten et al.
7,094,228 B2	8/2006	Zhang et al.	7,943,604 B2	5/2011	Coelingh Bennink et al.
7,097,853 B1	8/2006	Garbe et al.	7,945,459 B2	5/2011	Grace et al.
7,101,342 B1	9/2006	Caillouetie	7,960,368 B2	6/2011	Nickisch et al.
7,105,573 B2	9/2006	Krajcik et al.	7,989,436 B2	8/2011	Hill et al.
7,135,190 B2	11/2006	Piao et al.	7,989,487 B2	8/2011	Welsh et al.
7,153,522 B1	12/2006	Ikeura et al.	8,022,053 B2	9/2011	Mueller et al.
7,163,681 B2	1/2007	Giles-Komar et al.	8,048,017 B2	11/2011	Xu
7,163,699 B2	1/2007	Besse	8,048,869 B2	11/2011	Bunschoten et al.
7,175,850 B2	2/2007	Cevc	8,063,030 B2	11/2011	Ellman
7,179,799 B2	2/2007	Hill et al.	8,071,576 B2	12/2011	Coelingh et al.
7,196,074 B2	3/2007	Blye et al.	8,071,729 B2	12/2011	Giles-Komar et al.
7,198,800 B1	4/2007	Ko	8,075,916 B2	12/2011	Song et al.
7,198,801 B2	4/2007	Carrara et al.	8,075,917 B2	12/2011	Chung et al.
7,226,910 B2	6/2007	Wilson et al.	8,076,317 B2	12/2011	Kulmann
7,247,625 B2	7/2007	Zhang et al.	8,076,319 B2	12/2011	Leonard
7,250,446 B2	7/2007	Sang Ita et al.	8,080,553 B2	12/2011	Keith et al.
7,267,829 B2	9/2007	Kirby et al.	8,088,605 B2	1/2012	Beaudet et al.
7,300,926 B2	11/2007	Prokai et al.	8,096,940 B2	1/2012	Josephson et al.
7,303,763 B2	12/2007	Ho	8,101,209 B2	1/2012	Legrand et al.
7,317,037 B2	1/2008	Fensome et al.	8,101,773 B2	1/2012	Smith et al.
7,329,654 B2	2/2008	Kanojia et al.	8,114,152 B2	2/2012	Furst
7,335,650 B2	2/2008	Potter et al.	8,114,434 B2	2/2012	Sasaki et al.
7,374,779 B2	5/2008	Chen et al.	8,114,442 B2	2/2012	Tucker et al.
7,378,404 B2	5/2008	Peters et al.	8,119,741 B2	2/2012	Pavlin
7,381,427 B2	6/2008	Ancira et al.	8,121,886 B2	2/2012	Azar
7,388,006 B2	6/2008	Schmees et al.	8,124,118 B2	2/2012	Lennernas et al.
7,387,789 B2	7/2008	Klose et al.	8,124,595 B2	2/2012	Boissonneault
7,414,043 B2	8/2008	Kosemund et al.	8,147,561 B2	4/2012	Binmoeller
7,427,413 B2	9/2008	Savoir et al.	8,148,546 B2	4/2012	Schuster et al.
7,427,609 B2	9/2008	Leonard	8,158,613 B2	4/2012	Staniforth et al.
7,429,576 B2	9/2008	Labrie	8,158,614 B2	4/2012	Lambert et al.
7,431,941 B2	10/2008	Besins et al.	8,163,722 B2	4/2012	Savoir et al.
7,456,159 B2	11/2008	Houze et al.	8,177,449 B2	5/2012	Bayly et al.
7,459,445 B2	12/2008	Hill et al.	8,182,833 B2	5/2012	Hermesmyer
7,465,587 B2	12/2008	Imrich	8,187,615 B2	5/2012	Friedman
7,470,433 B2	12/2008	Carrara et al.	8,195,403 B2	6/2012	Ishikawa et al.
7,485,666 B2	2/2009	Villanueva et al.	8,202,736 B2	6/2012	Mousa et al.
7,497,855 B2	3/2009	Ausiello et al.	8,217,024 B2	7/2012	Ahmed et al.
7,498,303 B2	3/2009	Arnold et al.	8,221,785 B2	7/2012	Chien
7,534,765 B2	5/2009	Gregg et al.	8,222,008 B2	7/2012	Thoene
7,534,780 B2	5/2009	Wyrwa et al.	8,222,237 B2	7/2012	Nickisch et al.
7,550,142 B2	6/2009	Giles-Komar et al.	8,227,454 B2	7/2012	Hill et al.
7,563,565 B1	7/2009	Matsuo et al.	8,227,509 B2	7/2012	Castro et al.
7,569,274 B2	8/2009	Besse et al.	8,241,664 B2	8/2012	Dudley et al.
7,572,779 B2	8/2009	Al08a et al.	8,247,393 B2	8/2012	Ahmed et al.
7,572,780 B2	8/2009	Hermesmyer	8,257,724 B2	9/2012	Cromack et al.
7,589,082 B2	9/2009	Savoir et al.	8,257,725 B2	9/2012	Cromack et al.
7,671,027 B2	3/2010	Loumaye	8,268,352 B2	9/2012	Vaya et al.
7,674,783 B2	3/2010	Hermesmyer	8,268,806 B2	9/2012	Labrie
7,687,281 B2	3/2010	Roth et al.	8,268,878 B2	9/2012	Armer et al.
7,687,485 B2	3/2010	Levinson et al.	8,273,730 B2	9/2012	Fernandez et al.
7,694,683 B2	4/2010	Callister et al.	8,287,888 B2	10/2012	Song et al.
7,704,983 B1	4/2010	Hodgen et al.	8,288,366 B2	10/2012	Chochinov et al.
7,727,720 B2	6/2010	Dhallan	8,318,898 B2	11/2012	Fasel et al.
7,732,408 B2	6/2010	Josephson et al.	8,324,193 B2	12/2012	Lee-Sepsick et al.
7,749,989 B2	7/2010	Hill et al.	8,329,680 B2	12/2012	Evans et al.
7,767,656 B2	8/2010	Shoichet et al.	8,337,814 B2	12/2012	Osbakken et al.
7,799,769 B2	9/2010	White et al.	8,344,007 B2	1/2013	Tang et al.
7,815,936 B2	10/2010	Hasenzahl et al.	8,349,820 B2	1/2013	Zeun et al.
7,815,949 B2	10/2010	Cohen	8,353,863 B2	1/2013	Imran
			8,357,723 B2	1/2013	Satyam
			8,361,995 B2	1/2013	Schramm
			8,362,091 B2	1/2013	Tamarkin et al.
			8,372,424 B2	2/2013	Berry et al.

## US 10,639,375 B2

Page 5

(56)

## References Cited

## U.S. PATENT DOCUMENTS

8,372,806 B2	2/2013	Bohler et al.	2001/0031747 A1	10/2001	deZiegler et al.
8,377,482 B2	2/2013	Laurie et al.	2001/0032125 A1	10/2001	Bhan et al.
8,377,994 B2	2/2013	Gray et al.	2001/0034340 A1	10/2001	Pickar
8,394,759 B2	3/2013	Barathur et al.	2001/0053383 A1	12/2001	Miranda et al.
8,435,561 B2	3/2013	Besins et al.	2001/0056068 A1	12/2001	Chwalisz et al.
8,415,332 B2	4/2013	Diliberti et al.	2002/0012710 A1	1/2002	Lansky
8,420,111 B2	4/2013	Hermesmeyer	2002/0026158 A1	2/2002	Rathbone et al.
8,435,972 B2	5/2013	Stein et al.	2002/0028788 A1	3/2002	Bunt et al.
8,449,879 B2	5/2013	Laurent-Applegate et al.	2002/0035070 A1	3/2002	Gardlik et al.
8,450,108 B2	5/2013	Boyce	2002/0058648 A1	5/2002	Hammerly
8,454,945 B2	6/2013	McCook et al.	2002/0058926 A1	5/2002	Rathbone et al.
8,455,468 B2	6/2013	Hoffman et al.	2002/0064541 A1	5/2002	Lapidot et al.
8,461,138 B2	6/2013	Boissonneault	2002/0076441 A1	6/2002	Shin et al.
8,476,252 B2	7/2013	Achleitner et al.	2002/0102308 A1	8/2002	Wei et al.
8,481,488 B2	7/2013	Carter	2002/0107230 A1	8/2002	Waldon et al.
8,486,374 B2	7/2013	Tamarkin et al.	2002/0114803 A1	8/2002	Deaver et al.
8,486,442 B2	7/2013	Matsushita et al.	2002/0119174 A1	8/2002	Gardlik et al.
8,492,368 B2	7/2013	Vanlandingham et al.	2002/0119198 A1	8/2002	Gao et al.
8,507,467 B2	8/2013	Matsui et al.	2002/0132801 A1	9/2002	Heil et al.
8,512,693 B2	8/2013	Capito et al.	2002/0137749 A1	9/2002	Levinson et al.
8,512,754 B2	8/2013	Needham	2002/0142017 A1	10/2002	Simonnet
8,518,376 B2	8/2013	Tamarkin et al.	2002/0151530 A1	10/2002	Leonard et al.
8,536,159 B2	9/2013	Li et al.	2002/0156394 A1	10/2002	Mehrotra et al.
8,540,967 B2	9/2013	Barrett et al.	2002/0169150 A1	11/2002	Pickar
8,541,400 B2	9/2013	Johnsson et al.	2002/0169205 A1	11/2002	Chwalisz et al.
8,551,462 B2	10/2013	Goldstein et al.	2002/0173510 A1	11/2002	Levinson et al.
8,557,281 B2	10/2013	Halliday et al.	2002/0193356 A1	12/2002	Vanbeek et al.
8,568,374 B2	10/2013	De Graaff et al.	2002/0193758 A1	12/2002	Sandberg
8,591,951 B2	11/2013	Kohn et al.	2002/0197286 A1	12/2002	Brandman et al.
8,613,951 B2	12/2013	Zale et al.	2003/0003139 A1	1/2003	Lipp et al.
8,633,178 B2	1/2014	Bernick et al.	2003/0004145 A1	1/2003	Leonard
8,633,180 B2	1/2014	Li et al.	2003/0007994 A1	1/2003	Bunt et al.
8,636,787 B2	1/2014	Sabaria	2003/0027772 A1	2/2003	Breton
8,636,982 B2	1/2014	Tamarkin et al.	2003/0044453 A1	3/2003	Dittgen et al.
8,653,129 B2	2/2014	Fein et al.	2003/0049307 A1	3/2003	Gyurik
8,658,627 B2	2/2014	Voskuhl	2003/0064097 A1	4/2003	Patel et al.
8,658,628 B2	2/2014	Baucom	2003/0064975 A1	4/2003	Koch et al.
8,663,681 B2	3/2014	Nakamichi et al.	2003/0072760 A1	4/2003	Sirbasku
8,663,692 B1	3/2014	Mueller et al.	2003/0073248 A1	4/2003	Roth et al.
8,663,703 B2	3/2014	Lerner et al.	2003/0073673 A1	4/2003	Hesch
8,664,207 B2	3/2014	Li et al.	2003/0077297 A1	4/2003	Chen et al.
8,669,293 B2	3/2014	Levy et al.	2003/0078245 A1	4/2003	Bennink et al.
8,679,552 B2	3/2014	Guthery	2003/0091620 A1	5/2003	Fikstad et al.
8,694,358 B2	4/2014	Tryfon	2003/0091640 A1	5/2003	Raman A Than et al.
8,697,127 B2	4/2014	Sah	2003/0092691 A1	5/2003	Besse et al.
8,697,710 B2	4/2014	Li et al.	2003/0096012 A1	5/2003	Besse et al.
8,703,105 B2	4/2014	Tamarkin et al.	2003/0104048 A1	6/2003	Patel et al.
8,709,385 B2	4/2014	Tamarkin et al.	2003/0109507 A1	6/2003	Franke et al.
8,709,451 B2	4/2014	Rapoport et al.	2003/0113268 A1	6/2003	Buenafoe et al.
8,715,735 B2	5/2014	Funke et al.	2003/0114420 A1	6/2003	Salvati et al.
8,721,331 B2	5/2014	Raghuprasad	2003/0114430 A1	6/2003	Macleod et al.
8,722,021 B2	5/2014	Friedman et al.	2003/0124182 A1	7/2003	Shojaei et al.
8,734,846 B2	5/2014	Ali et al.	2003/0124191 A1	7/2003	Besse et al.
8,735,381 B2	5/2014	Podolski	2003/0130558 A1	7/2003	Massara et al.
8,741,336 B2	6/2014	Dipierro et al.	2003/0144258 A1	7/2003	Heil et al.
8,741,373 B2	6/2014	Bromley et al.	2003/0157157 A1	8/2003	Luo et al.
8,753,661 B2	6/2014	Steinmuller et al.	2003/0166509 A1	9/2003	Edwards et al.
8,784,882 B2	7/2014	Mattern	2003/0170295 A1	9/2003	Kim et al.
8,815,261 B2	8/2014	Hanma	2003/0175329 A1	9/2003	Azarnoff et al.
8,846,648 B2	9/2014	Bernick et al.	2003/0175333 A1	9/2003	Shefer et al.
8,846,649 B2	9/2014	Bernick et al.	2003/0180352 A1	9/2003	Patel et al.
8,933,059 B2	1/2015	Bernick et al.	2003/0181353 A1	9/2003	Nyce
8,987,237 B2	3/2015	Bernick et al.	2003/0181728 A1	9/2003	Salvati et al.
8,987,238 B2	3/2015	Bernick et al.	2003/0191096 A1	10/2003	Leonard et al.
8,993,548 B2	3/2015	Bernick et al.	2003/0195177 A1	10/2003	Leonard et al.
8,993,549 B2	3/2015	Bernick et al.	2003/0215496 A1	11/2003	Patel et al.
9,006,222 B2	4/2015	Bernick et al.	2003/0219402 A1	11/2003	Rutter
9,012,434 B2	4/2015	Bernick et al.	2003/0220297 A1	11/2003	Berstein et al.
9,289,382 B2	3/2016	Bernick et al.	2003/0224057 A1	12/2003	Martin-Letellier et al.
2001/0005728 A1	6/2001	Guittard et al.	2003/0224059 A1	12/2003	Lerner et al.
2001/0009673 A1	7/2001	Lipp et al.	2003/0225047 A1	12/2003	Caubel et al.
2001/0021816 A1	9/2001	Caillouetie	2003/0225048 A1	12/2003	Caubel et al.
2001/0023261 A1	9/2001	Ryoo et al.	2003/0225050 A1	12/2003	Eichardt et al.
2001/0027189 A1	10/2001	Bennink et al.	2003/0228686 A1	12/2003	Klausner et al.
2001/0029357 A1	10/2001	Bunt et al.	2003/0229057 A1	12/2003	Caubel et al.
			2003/0235596 A1	12/2003	Gao et al.
			2003/0236236 A1	12/2003	Chen et al.
			2004/0009960 A1	1/2004	Heil et al.
			2004/0022820 A1	2/2004	Anderson



## US 10,639,375 B2

Page 6

(56)

## References Cited

## U.S. PATENT DOCUMENTS

2004/0034001	A1	2/2004	Karara	2005/0220825	A1	10/2005	Funke et al.
2004/0037881	A1	2/2004	Guittard et al.	2005/0220900	A1	10/2005	Popp et al.
2004/0039356	A1	2/2004	Maki et al.	2005/0222106	A1	10/2005	Bracht
2004/0043043	A1	3/2004	Schlyter et al.	2005/0228692	A1	10/2005	Hodgdon
2004/0043943	A1	3/2004	Guittard et al.	2005/0228718	A1	10/2005	Austin
2004/0044080	A1	3/2004	Place et al.	2005/0239747	A1	10/2005	Yang et al.
2004/0048900	A1	3/2004	Flood	2005/0239758	A1	10/2005	Roby
2004/0052824	A1	3/2004	AbouChacra-Vernet et al.	2005/0244360	A1	11/2005	Billoni
2004/0073024	A1	4/2004	Metcalf, III et al.	2005/0244522	A1	11/2005	Carrara et al.
2004/0077605	A1	4/2004	Salvati et al.	2005/0245902	A1	11/2005	Cornish et al.
2004/0077606	A1	4/2004	Salvati et al.	2005/0250746	A1	11/2005	Iammatieo
2004/0087548	A1	5/2004	Salvati et al.	2005/0250750	A1	11/2005	Cummings et al.
2004/0087564	A1	5/2004	Wright et al.	2005/0250753	A1	11/2005	Fink et al.
2004/0089308	A1	5/2004	Welch	2005/0256028	A1	11/2005	Yun et al.
2004/0092494	A9	5/2004	Dudley	2005/0266078	A1	12/2005	Jorda et al.
2004/0092583	A1	5/2004	Shanahan-Prendergast	2005/0266088	A1	12/2005	Hinrichs et al.
2004/0093261	A1	5/2004	Jain et al.	2005/0271597	A1	12/2005	Keith
2004/0097468	A1	5/2004	Wimalawansa	2005/0271598	A1	12/2005	Friedman et al.
2004/0101557	A1	5/2004	Gibson et al.	2005/0272685	A1	12/2005	Hung
2004/0106542	A1	6/2004	Deaver et al.	2005/0272712	A1	12/2005	Grubb et al.
2004/0110732	A1	6/2004	Masini-Eteve et al.	2006/0009428	A1	1/2006	Grubb et al.
2004/0131670	A1	7/2004	Gao	2006/0014728	A1	1/2006	Chwalisz et al.
2004/0138103	A1	7/2004	Patt	2006/0018937	A1	1/2006	Friedman et al.
2004/0142012	A1	7/2004	Bunt et al.	2006/0019978	A1	1/2006	Balog
2004/0146539	A1	7/2004	Gupta	2006/0020002	A1	1/2006	Salvati et al.
2004/0146894	A1	7/2004	Warrington et al.	2006/0030615	A1	2/2006	Fensome et al.
2004/0161435	A1	8/2004	Gupta	2006/0034889	A1	2/2006	Jo et al.
2004/0176324	A1	9/2004	Salvati et al.	2006/0034904	A1	2/2006	Weimann
2004/0176336	A1	9/2004	Rodriguez	2006/0051391	A1	3/2006	Dvoskin et al.
2004/0185104	A1	9/2004	Piao et al.	2006/0052341	A1	3/2006	Cornish et al.
2004/0191207	A1	9/2004	Lipari et al.	2006/0069031	A1	3/2006	Loumaye
2004/0191276	A1	9/2004	Muni	2006/0078618	A1	4/2006	Constantinides et al.
2004/0198706	A1	10/2004	Carrara et al.	2006/0083778	A1	4/2006	Allison et al.
2004/0210280	A1	10/2004	Liedtke	2006/0084704	A1	4/2006	Shih et al.
2004/0213744	A1	10/2004	Lulla et al.	2006/0088580	A1	4/2006	Meconi et al.
2004/0219124	A1	11/2004	Gupta	2006/0089337	A1	4/2006	Casper et al.
2004/0225140	A1	11/2004	Fernandez et al.	2006/0093678	A1	5/2006	Chickering, III et al.
2004/0234606	A1	11/2004	Levine et al.	2006/0100180	A1	5/2006	Nubbemeyer et al.
2004/0241219	A1	12/2004	Hille et al.	2006/0106004	A1	5/2006	Brody et al.
2004/0243437	A1	12/2004	Grace et al.	2006/0110415	A1	5/2006	Gupta
2004/0253319	A1	12/2004	Netke et al.	2006/0111424	A1	5/2006	Salvati et al.
2004/0259817	A1	12/2004	Waldon et al.	2006/0121102	A1	6/2006	Chiang
2004/0266745	A1	12/2004	Schwanitz et al.	2006/0121626	A1	6/2006	Imrich
2005/0003003	A1	1/2005	Basu et al.	2006/0134188	A1	6/2006	Podhaisky et al.
2005/0004088	A1	1/2005	Hesch	2006/0135619	A1	6/2006	Kick et al.
2005/0009800	A1	1/2005	Thumbbeck et al.	2006/0165744	A1	7/2006	Jamil et al.
2005/0014729	A1	1/2005	Pulaski	2006/0193789	A1	8/2006	Tamarkin et al.
2005/0020550	A1	1/2005	Morris et al.	2006/0194775	A1	8/2006	Tofovic et al.
2005/0020552	A1	1/2005	Aschkenasay et al.	2006/0204557	A1	9/2006	Gupta et al.
2005/0021009	A1	1/2005	Massara et al.	2006/0233743	A1	10/2006	Kelly
2005/0025833	A1	2/2005	Aschkenasay et al.	2006/0233841	A1	10/2006	Brodbeck et al.
2005/0031651	A1	2/2005	Gervais et al.	2006/0235037	A1	10/2006	Purandare et al.
2005/0042173	A1	2/2005	Besse et al.	2006/0240111	A1	10/2006	Fernandez et al.
2005/0042268	A1	2/2005	Aschkenasay et al.	2006/0246122	A1	11/2006	Langguth et al.
2005/0048116	A1	3/2005	Straub et al.	2006/0247216	A1	11/2006	Haj-Yehia
2005/0054991	A1	3/2005	Tobyn et al.	2006/0247221	A1	11/2006	Coelingh Bennink et al.
2005/0079138	A1	4/2005	Chickering, III et al.	2006/0251581	A1	11/2006	McIntyre et al.
2005/0085453	A1	4/2005	Govindarajan	2006/0252049	A1	11/2006	Shuler et al.
2005/0101579	A1	5/2005	Shippen	2006/0257472	A1	11/2006	Neilsen
2005/0113350	A1	5/2005	Duesterberg et al.	2006/0275218	A1	12/2006	Tamarkin et al.
2005/0118244	A1	6/2005	Theobald et al.	2006/0275360	A1	12/2006	Ahmed et al.
2005/0118272	A1	6/2005	Besse et al.	2006/0276414	A1	12/2006	Coelingh Bennink et al.
2005/0129756	A1	6/2005	Podhaisky et al.	2006/0280771	A1	12/2006	Groenewegen et al.
2005/0152956	A1	7/2005	Dudley	2006/0280797	A1	12/2006	Shoichet et al.
2005/0153946	A1	7/2005	Hirsh et al.	2006/0280800	A1	12/2006	Nagi et al.
2005/0164977	A1	7/2005	Coelingh Bennink	2006/0292223	A1	12/2006	Woolfson et al.
2005/0182105	A1	8/2005	Nirschl et al.	2007/0004693	A1	1/2007	Woolfson et al.
2005/0186141	A1	8/2005	Gonda et al.	2007/0004694	A1	1/2007	Woolfson et al.
2005/0187267	A1	8/2005	Hamann et al.	2007/0009559	A1	1/2007	Li et al.
2005/0192253	A1	9/2005	Salvati et al.	2007/0009594	A1	1/2007	Grubb et al.
2005/0192310	A1	9/2005	Gavai et al.	2007/0010550	A1	1/2007	McKenzie
2005/0196434	A1	9/2005	Brierre	2007/0014839	A1	1/2007	Bracht
2005/0207990	A1	9/2005	Funke et al.	2007/0015698	A1	1/2007	Kleinman et al.
2005/0209209	A1	9/2005	Koch et al.	2007/0021360	A1	1/2007	Nyce et al.
2005/0214384	A1	9/2005	Juturu et al.	2007/0027201	A1	2/2007	McComas et al.
				2007/0031491	A1	2/2007	Levine et al.
				2007/0037780	A1	2/2007	Ebert et al.
				2007/0037782	A1	2/2007	Hibino et al.
				2007/0042038	A1	2/2007	Besse

## US 10,639,375 B2

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(56)

## References Cited

## U.S. PATENT DOCUMENTS

2007/0060589	A1	3/2007	Purandare et al.	2008/0255089	A1	10/2008	Kat Am Reddy
2007/0066628	A1	3/2007	Zhang et al.	2008/0261931	A1	10/2008	Hedner et al.
2007/0066637	A1	3/2007	Zhang et al.	2008/0299220	A1	12/2008	Tamarkin et al.
2007/0066675	A1	3/2007	Zhang et al.	2008/0306036	A1	12/2008	Katamreddy
2007/0078091	A1	4/2007	Hubler et al.	2008/0312197	A1	12/2008	Rodriguez
2007/0088029	A1	4/2007	Balog et al.	2008/0312198	A1	12/2008	Rodriguez
2007/0093548	A1	4/2007	Diffendal et al.	2008/0319078	A1	12/2008	Katamreddy
2007/0116729	A1	5/2007	Palepu	2009/0004246	A1	1/2009	Woolfson et al.
2007/0116829	A1	5/2007	Prakash et al.	2009/0010968	A1	1/2009	Allart et al.
2007/0128263	A1	6/2007	Gargiulo et al.	2009/0011041	A1	1/2009	Musaeva et al.
2007/0154533	A1	7/2007	Dudley	2009/0017120	A1	1/2009	Trimble et al.
2007/0167418	A1	7/2007	Ferguson	2009/0022683	A1	1/2009	Song et al.
2007/0178166	A1	8/2007	Bernstein et al.	2009/0047357	A1	2/2009	Tomohira et al.
2007/0184558	A1	8/2007	Roth et al.	2009/0053294	A1	2/2009	Prendergast
2007/0185068	A1	8/2007	Ferguson et al.	2009/0060982	A1	3/2009	Ron et al.
2007/0190022	A1	8/2007	Bacopoulos et al.	2009/0060997	A1	3/2009	Seitz et al.
2007/0191319	A1	8/2007	Ke et al.	2009/0068118	A1	3/2009	Eini et al.
2007/0196415	A1	8/2007	Chen et al.	2009/0074859	A1	3/2009	Patel
2007/0196433	A1	8/2007	Ron et al.	2009/0081206	A1	3/2009	Leibovitz
2007/0207225	A1	9/2007	Squadrito	2009/0081278	A1	3/2009	De Graaff et al.
2007/0225281	A1	9/2007	Zhang et al.	2009/0081303	A1	3/2009	Savoir et al.
2007/0232574	A1	10/2007	Galey et al.	2009/0092656	A1	4/2009	Klamerus et al.
2007/0238713	A1	10/2007	Gast et al.	2009/0093440	A1	4/2009	Murad
2007/0243229	A1	10/2007	Smith et al.	2009/0098069	A1	4/2009	Vacca
2007/0248658	A1	10/2007	Zurdo Schroeder et al.	2009/0099106	A1	4/2009	Phiasivongsa et al.
2007/0254858	A1	11/2007	Cronk	2009/0099149	A1	4/2009	Liu et al.
2007/0255197	A1	11/2007	Humberstone et al.	2009/0130029	A1	5/2009	Tamarkin et al.
2007/0264309	A1	11/2007	Chollet et al.	2009/0131385	A1	5/2009	Voskuhl
2007/0264345	A1	11/2007	Eros et al.	2009/0137478	A1	5/2009	Bernstein et al.
2007/0264349	A1	11/2007	Lee et al.	2009/0137538	A1	5/2009	Klamerus et al.
2007/0286819	A1	12/2007	DeVries et al.	2009/0143344	A1	6/2009	Chang
2007/0287688	A1	12/2007	Chan et al.	2009/0164341	A1	6/2009	Sunvold et al.
2007/0287789	A1	12/2007	Jones et al.	2009/0175799	A1	7/2009	Tamarkin et al.
2007/0292359	A1	12/2007	Friedman et al.	2009/0181088	A1	7/2009	Song et al.
2007/0292387	A1	12/2007	Jon et al.	2009/0186081	A1	7/2009	Holm et al.
2007/0292461	A1	12/2007	Tamarkin et al.	2009/0197843	A1	8/2009	Notelovitz et al.
2007/0292493	A1	12/2007	Brierre	2009/0203658	A1	8/2009	Marx et al.
2007/0298089	A1	12/2007	Saeki et al.	2009/0214474	A1	8/2009	Jennings
2008/0026035	A1	1/2008	Chollet et al.	2009/0227025	A1	9/2009	Nichols et al.
2008/0026040	A1	1/2008	Farr et al.	2009/0227550	A1	9/2009	Mattern
2008/0026062	A1	1/2008	Farr et al.	2009/0232897	A1	9/2009	Sahoo et al.
2008/0038219	A1	2/2008	Mosbaugh et al.	2009/0258096	A1	10/2009	Cohen
2008/0038350	A1	2/2008	Gerecke et al.	2009/0264395	A1	10/2009	Creasy
2008/0039405	A1	2/2008	Langley et al.	2009/0269403	A1	10/2009	Shaked et al.
2008/0050317	A1	2/2008	Tamarkin et al.	2009/0285772	A1	11/2009	Phiasivongsa et al.
2008/0051351	A1	2/2008	Ghisalberti	2009/0285869	A1	11/2009	Trimble
2008/0063607	A1	3/2008	Tamarkin et al.	2009/0318558	A1	12/2009	Kim et al.
2008/0069779	A1	3/2008	Tamarkin et al.	2009/0324714	A1	12/2009	Liu et al.
2008/0069791	A1	3/2008	Beissert	2009/0325916	A1	12/2009	Zhang et al.
2008/0085877	A1	4/2008	Bortz	2010/0008985	A1	1/2010	Pellikaan et al.
2008/0095831	A1	4/2008	Mc Graw	2010/0028360	A1	2/2010	Atwood
2008/0095838	A1	4/2008	Abou Chacra-Vernet	2010/0034838	A1	2/2010	Staniforth et al.
2008/0113953	A1	5/2008	De Vries et al.	2010/0034880	A1	2/2010	Sintov et al.
2008/0114050	A1	5/2008	Fensome et al.	2010/0040671	A1	2/2010	Ahmed et al.
2008/0119537	A1	5/2008	Zhang et al.	2010/0048523	A1	2/2010	Bachman et al.
2008/0125402	A1	5/2008	Dilberti	2010/0055138	A1	3/2010	Margulies et al.
2008/0138379	A1	6/2008	Jennings-Spring	2010/0074959	A1	3/2010	Hansom et al.
2008/0138390	A1	6/2008	Hsu et al.	2010/0086501	A1	4/2010	Chang et al.
2008/0139392	A1	6/2008	Acosta-Zara et al.	2010/0086599	A1	4/2010	Huempel et al.
2008/0145423	A1	6/2008	Khan et al.	2010/0092568	A1	4/2010	Lerner et al.
2008/0153789	A1	6/2008	Dmowski et al.	2010/0105071	A1	4/2010	Laufer et al.
2008/0175814	A1	7/2008	Phiasivongsa et al.	2010/0119585	A1	5/2010	Hille et al.
2008/0175905	A1	7/2008	Liu et al.	2010/0129320	A1	5/2010	Phiasivongsa et al.
2008/0175908	A1	7/2008	Liu et al.	2010/0136105	A1	6/2010	Chen et al.
2008/0188829	A1	8/2008	Creasy	2010/0137265	A1	6/2010	Leonard
2008/0206156	A1	8/2008	Cronk	2010/0137271	A1	6/2010	Chen et al.
2008/0206159	A1	8/2008	Tamarkin et al.	2010/0143420	A1	6/2010	Shenoy et al.
2008/0206161	A1	8/2008	Tamarkin et al.	2010/0143481	A1	6/2010	Shenoy et al.
2008/0214512	A1	9/2008	Seitz et al.	2010/0150993	A1	6/2010	Theobald et al.
2008/0220069	A1	9/2008	Allison	2010/0152144	A1	6/2010	Hermismeyer
2008/0226698	A1	9/2008	Tang et al.	2010/0168228	A1	7/2010	Bose et al.
2008/0227763	A1	9/2008	Lanquetin et al.	2010/0183723	A1	7/2010	Laurent-Applegate et al.
2008/0234199	A1	9/2008	Kat Am Reddy	2010/0184736	A1	7/2010	Coelingh Bennink et al.
2008/0234240	A1	9/2008	Duesterberg et al.	2010/0190758	A1	7/2010	Fauser et al.
2008/0255078	A1	10/2008	Kat Am Reddy	2010/0204326	A1	8/2010	D'Souza
				2010/0210994	A1	8/2010	Zarif
				2010/0221195	A1	9/2010	Tamarkin et al.
				2010/0227797	A1	9/2010	Axelsson et al.
				2010/0240626	A1	9/2010	Kulkarni et al.

## US 10,639,375 B2

Page 8

(56)	<b>References Cited</b>				
	U.S. PATENT DOCUMENTS				
2010/0247482	A1	9/2010	Cui et al.	2012/0065221	A1 3/2012 Babul
2010/0247632	A1	9/2010	Dong et al.	2012/0087872	A1 4/2012 Tamarkin et al.
2010/0247635	A1	9/2010	Rosenberg et al.	2012/0101073	A1 4/2012 Mannion et al.
2010/0255085	A1	10/2010	Liu et al.	2012/0121517	A1 5/2012 Song et al.
2010/0273730	A1	10/2010	Hsu et al.	2012/0121692	A1 5/2012 Xu et al.
2010/0278759	A1	11/2010	Murad	2012/0122829	A1 5/2012 Taravella et al.
2010/0279988	A1	11/2010	Setiawan et al.	2012/0128625	A1 5/2012 Shalwitz et al.
2010/0291191	A1	11/2010	Shoichet et al.	2012/0128654	A1 5/2012 Terpstra et al.
2010/0292199	A1	11/2010	Leverd et al.	2012/0128683	A1 5/2012 Shantha
2010/0303825	A9	12/2010	Sirbasku	2012/0128733	A1 5/2012 Perrin et al.
2010/0312137	A1	12/2010	Gilmour et al.	2012/0128777	A1 5/2012 Keck et al.
2010/0316724	A1	12/2010	Whitfield et al.	2012/0129773	A1 5/2012 Geier et al.
2010/0322884	A1	12/2010	Dipietro et al.	2012/0129819	A1 5/2012 Vancaillie et al.
2010/0330168	A1	12/2010	Gicquel et al.	2012/0136013	A1 5/2012 Li et al.
2011/0028439	A1	2/2011	Witt-Enderby et al.	2012/0142645	A1 6/2012 Marx
2011/0039814	A1	2/2011	Huatan et al.	2012/0148670	A1 6/2012 Kim et al.
2011/0053845	A1	3/2011	Levine et al.	2012/0149748	A1 6/2012 Shanler et al.
2011/0066473	A1	3/2011	Bernick et al.	2012/0172343	A1 7/2012 Lindenthal et al.
2011/0076775	A1	3/2011	Stewart et al.	2012/0184515	A1 7/2012 Klar et al.
2011/0076776	A1	3/2011	Stewart et al.	2012/0231052	A1 9/2012 Sitruk-Ware et al.
2011/0086825	A1	4/2011	Chatroux	2012/0232042	A1 9/2012 Kneissel et al.
2011/0087192	A1	4/2011	Uhland et al.	2012/0263679	A1 10/2012 Marlow et al.
2011/0091555	A1	4/2011	De Luigi Bruschi et al.	2012/0269721	A1 10/2012 Weng et al.
2011/0098258	A1	4/2011	Masini-Eteve et al.	2012/0269878	A2 10/2012 Cantor et al.
2011/0098631	A1	4/2011	Mcintyre et al.	2012/0277249	A1 11/2012 Andersson et al.
2011/0104268	A1	5/2011	Pachot et al.	2012/0277727	A1 11/2012 Doshi et al.
2011/0104289	A1	5/2011	Sa Voir Vilboeuf et al.	2012/0283671	A1 11/2012 Shibata et al.
2011/0130372	A1	6/2011	Agostinacchio et al.	2012/0295911	A1 11/2012 Mannion et al.
2011/0135719	A1	6/2011	Besins	2012/0301517	A1 11/2012 Zhang et al.
2011/0142945	A1	6/2011	Chen et al.	2012/0301538	A1 11/2012 Gordon-Beresford et al.
2011/0152840	A1	6/2011	Lee et al.	2012/0302535	A1 11/2012 Caufriez et al.
2011/0158920	A1	6/2011	Morley et al.	2012/0316130	A1 12/2012 Hendrix
2011/0171140	A1	7/2011	Illum et al.	2012/0316496	A1 12/2012 Hoffmann et al.
2011/0182997	A1	7/2011	Lewis et al.	2012/0321579	A1 12/2012 Edelson et al.
2011/0190201	A1	8/2011	Hyde et al.	2012/0322779	A9 12/2012 Voskuhl
2011/0195031	A1	8/2011	Du	2012/0328549	A1 12/2012 Edelson et al.
2011/0195114	A1	8/2011	Carrara et al.	2012/0329738	A1 12/2012 Liu
2011/0195944	A1	8/2011	Mura et al.	2013/0004619	A1 1/2013 Chow et al.
2011/0217341	A1	9/2011	Sah	2013/0011342	A1 1/2013 Tamarkin et al.
2011/0238003	A1	9/2011	Bruno-Raimondi et al.	2013/0017239	A1 1/2013 Viladot Petit et al.
2011/0244043	A1	10/2011	Xu et al.	2013/0022674	A1 1/2013 Dudley et al.
2011/0250256	A1	10/2011	Hyun-Oh et al.	2013/0023505	A1 1/2013 Garfield et al.
2011/0250259	A1	10/2011	Buckman	2013/0023823	A1 1/2013 Simpson et al.
2011/0250274	A1	10/2011	Shaked et al.	2013/0028850	A1 1/2013 Tamarkin et al.
2011/0256092	A1	10/2011	Phiasivongsa et al.	2013/0029947	A1 1/2013 Nachaegari et al.
2011/0262373	A1	10/2011	Umbert Millet	2013/0029957	A1 1/2013 Giliyar et al.
2011/0262494	A1	10/2011	Achleitner et al.	2013/0045266	A1 2/2013 Choi et al.
2011/0268665	A1	11/2011	Tamarkin et al.	2013/0045953	A1 2/2013 Sitruk-Ware et al.
2011/0275584	A1	11/2011	Wilckens et al.	2013/0059795	A1 3/2013 Lo et al.
2011/0281832	A1	11/2011	Li et al.	2013/0064897	A1 3/2013 Binay
2011/0287094	A1	11/2011	Penhasi et al.	2013/0072466	A1 3/2013 Choi et al.
2011/0293720	A1	12/2011	General et al.	2013/0084257	A1 4/2013 Ishida et al.
2011/0294738	A1	12/2011	Ren et al.	2013/0085123	A1 4/2013 Li et al.
2011/0300167	A1	12/2011	McMurry et al.	2013/0089574	A1 4/2013 Schmidt-Gollwitzer et al.
2011/0301087	A1	12/2011	McBride et al.	2013/0090318	A1 4/2013 Ulmann et al.
2011/0306579	A1	12/2011	Stein	2013/0102781	A1 4/2013 Bevill et al.
2011/0311592	A1	12/2011	Birbara	2013/0108551	A1 5/2013 Langereis et al.
2011/0312928	A1	12/2011	Nachaegari et al.	2013/0116215	A1 5/2013 Coma et al.
2011/0318405	A1	12/2011	Erwin	2013/0116222	A1 5/2013 Arnold et al.
2011/0318431	A1	12/2011	Gulati	2013/0122051	A1 5/2013 Abidi et al.
2012/0009276	A1	1/2012	DeGroote	2013/0123175	A1 5/2013 Hill et al.
2012/0015350	A1	1/2012	Nabatiyan et al.	2013/0123220	A1 5/2013 Queiroz
2012/0021041	A1	1/2012	Rossi et al.	2013/0123351	A1 5/2013 Dewitt
2012/0028888	A1	2/2012	Janz et al.	2013/0129818	A1 5/2013 Bernick et al.
2012/0028910	A1	2/2012	Combal et al.	2013/0131027	A1 5/2013 Pakkalin et al.
2012/0028936	A1	2/2012	Gloger et al.	2013/0131028	A1 5/2013 Snyder et al.
2012/0045532	A1	2/2012	Cohen	2013/0131029	A1 5/2013 Bakker et al.
2012/0046264	A1	2/2012	Simes et al.	2013/0149314	A1 6/2013 Bullerdiek et al.
2012/0046518	A1	2/2012	Yoakum et al.	2013/0164225	A1 6/2013 Tamarkin et al.
2012/0052077	A1	3/2012	Truitt, III et al.	2013/0164346	A1 6/2013 Lee et al.
2012/0058171	A1	3/2012	De Graaff et al.	2013/0165744	A1 6/2013 Carson et al.
2012/0058962	A1	3/2012	Cumming et al.	2013/0178452	A1 7/2013 King
2012/0058979	A1	3/2012	Keith et al.	2013/0183254	A1 7/2013 Zhou et al.
2012/0064135	A1	3/2012	Levin et al.	2013/0183325	A1 7/2013 Bottoni et al.
2012/0065179	A1	3/2012	Andersson	2013/0189193	A1 7/2013 Tamarkin et al.
				2013/0189196	A1 7/2013 Tamarkin et al.
				2013/0189230	A1 7/2013 Shoichet et al.
				2013/0189368	A1 7/2013 Mosqueira et al.

## US 10,639,375 B2

Page 9

(56)

## References Cited

## FOREIGN PATENT DOCUMENTS

U.S. PATENT DOCUMENTS					
			CA	2856520	A1 5/2013
			CN	102258455	11/2011
			CN	102258455	A 11/2011
2013/0210709	A1	8/2013	EP	0275716	A1 7/1988
2013/0216550	A1	8/2013	EP	0622075	A1 2/1994
2013/0216596	A1	8/2013	EP	0622075	A1 11/1994
2013/0224177	A1	8/2013	EP	0785211	A1 1/1996
2013/0224257	A1	8/2013	EP	0785212	A1 1/1996
2013/0224268	A1	8/2013	EP	0811381	6/1997
2013/0224300	A1	8/2013	EP	0785211	A1 7/1997
2013/0225412	A1	8/2013	EP	0785212	A1 7/1997
2013/0225542	A1	8/2013	EP	0811381	B1 5/2003
2013/0226113	A1	8/2013	EP	1094781	B1 7/2006
2013/0243696	A1	9/2013	EP	2191833	6/2010
2013/0245253	A1	9/2013	EP	2191833	B1 2/2013
2013/0245570	A1	9/2013	EP	452238	A 8/1936
2013/0261096	A1	10/2013	GB	720561	12/1954
2013/0266645	A1	10/2013	GB	720561	A 12/1954
2013/0267485	A1	10/2013	GB	848881	A 9/1960
2013/0273167	A1	10/2013	GB	874368	8/1961
2013/0274211	A1	10/2013	GB	874368	A 8/1961
2013/0280213	A1	10/2013	GB	1589946	A 5/1981
2013/0316374	A1	11/2013	IN	216026	3/2008
2013/0317065	A1	11/2013	IN	2005K000053	9/2009
2013/0317315	A1	11/2013	IN	244217	11/2010
2013/0324565	A1	12/2013	JP	2007-516259	A 6/2007
2013/0331363	A1	12/2013	JP	2009-510127	A 3/2009
2013/0338122	A1	12/2013	MX	2014/006256	A 10/2014
2013/0338123	A1	12/2013	WO	WO-1990011064	A1 10/1990
2013/0338124	A1	12/2013	WO	WO-1993017686	A1 9/1993
2013/0345187	A1	12/2013	WO	WO-1994022426	A1 3/1994
2014/0018335	A1	1/2014	WO	WO-1995030409	A1 11/1995
2014/0024590	A1	1/2014	WO	WO-1996009826	A2 4/1996
2014/0031289	A1	1/2014	WO	WO-9619975	A1 7/1996
2014/0031323	A1	1/2014	WO	WO-1996030000	A1 10/1996
2014/0066416	A1	3/2014	WO	WO-9705491	2/1997
2014/0072531	A1	3/2014	WO	WO-1997043989	A1 11/1997
2014/0079686	A1	3/2014	WO	WO-1998010293	A1 3/1998
2014/0088051	A1	3/2014	WO	WO-1998032465	A1 7/1998
2014/0088058	A1	3/2014	WO	WO-1998051280	A1 11/1998
2014/0088059	A1	3/2014	WO	WO-1999039700	A1 2/1999
2014/0094426	A1	4/2014	WO	WO-1999032072	A1 7/1999
2014/0094440	A1	4/2014	WO	WO-9939700	A1 8/1999
2014/0094441	A1	4/2014	WO	WO-1999042109	A1 8/1999
2014/0099362	A1	4/2014	WO	WO-9943304	9/1999
2014/0100159	A1	4/2014	WO	WO-1999048477	A1 9/1999
2014/0100204	A1	4/2014	WO	WO-1999053910	A2 10/1999
2014/0100205	A1	4/2014	WO	WO-1999063974	A2 12/1999
2014/0100206	A1	4/2014	WO	WO-2000001351	A1 1/2000
2014/0113889	A1	4/2014	WO	WO-2000006175	A1 2/2000
2014/0127185	A1	5/2014	WO	WO-2000045795	A2 8/2000
2014/0127280	A1	5/2014	WO	WO-2000050007	A1 8/2000
2014/0127308	A1	5/2014	WO	WO-2000059577	A1 10/2000
2014/0128798	A1	5/2014	WO	WO-2000038659	A1 11/2000
2014/0148491	A1	5/2014	WO	WO-2001037808	A1 11/2000
2014/0186332	A1	7/2014	WO	WO-2000076522	A1 12/2000
2014/0187487	A1	7/2014	WO	WO-2002007700	A2 7/2001
2014/0193523	A1	7/2014	WO	WO-2001054699	A1 8/2001
2014/0194396	A1	7/2014	WO	WO-2001060325	A1 8/2001
2014/0206616	A1	7/2014	WO	WO-2002011768	A1 2/2002
2014/0213565	A1	7/2014	WO	WO-2002022132	A2 3/2002
2014/0288035	A1	9/2014	WO	WO-0241878	A2 5/2002
2014/0329783	A1	11/2014	WO	WO-2002040008	A1 5/2002
2014/0335193	A1	11/2014	WO	WO-2002053131	A1 7/2002
2014/0370084	A1	12/2014	WO	WO-2002078602	A3 2/2003
2014/0371182	A1	12/2014	WO	WO-03028667	A2 4/2003
2014/0371183	A1	12/2014	WO	WO-2003041718	A1 5/2003
2014/0371184	A1	12/2014	WO	WO-2003041741	A1 5/2003
2014/0371185	A1	12/2014	WO	WO-2003068186	A1 8/2003
2015/0031654	A1	1/2015	WO	WO-2003077923	A1 9/2003
2015/0045335	A1	2/2015	WO	WO-2003082254	A1 10/2003
2015/0133421	A1	5/2015	WO	WO-2002078604	A3 11/2003
2015/0196640	A1	7/2015	WO	WO-2003092588	A2 11/2003
2015/0202211	A1	7/2015	WO	WO-2004014397	A1 2/2004
2017/0340739	A1	11/2017	WO	WO-2004014432	A1 2/2004
			WO	WO-2004017983	A1 3/2004
			WO	WO-2005027911	A1 3/2004



## US 10,639,375 B2

Page 10

## (56) References Cited

## FOREIGN PATENT DOCUMENTS

WO WO-2004032897 A2 4/2004  
 WO WO-2004052336 A2 6/2004  
 WO WO-2005120517 A1 6/2004  
 WO WO-2004054540 A2 7/2004  
 WO WO-2004080413 A2 9/2004  
 WO WO-2005030175 A1 4/2005  
 WO WO-2005081825 A2 9/2005  
 WO WO-2005087194 A1 9/2005  
 WO WO-2005087199 A2 9/2005  
 WO WO-2005105059 A1 11/2005  
 WO WO-2005115335 A1 12/2005  
 WO WO-2005120470 A1 12/2005  
 WO WO-2005120517 A1 12/2005  
 WO WO-2006013369 A2 2/2006  
 WO WO-2006034090 A1 3/2006  
 WO WO-2006036899 A2 4/2006  
 WO WO-2006053172 A2 5/2006  
 WO WO-2006105615 A1 10/2006  
 WO WO-2006113505 A2 10/2006  
 WO WO-2006138686 A1 12/2006  
 WO WO-2006138735 A2 12/2006  
 WO WO 2007/038796 A1 4/2007  
 WO WO-2007045027 A1 4/2007  
 WO WO-2007103294 A2 9/2007  
 WO WO-2006138735 A3 10/2007  
 WO WO-2007120868 A2 10/2007  
 WO WO-007124250 A2 11/2007  
 WO WO-2007123790 A1 11/2007  
 WO WO-007144151 A1 12/2007  
 WO WO-2006138686 A1 12/2007  
 WO WO-2007124250 A3 12/2007  
 WO WO-2007144151 A1 12/2007  
 WO WO-2007103294 A3 4/2008  
 WO WO-2008049516 A3 5/2008  
 WO WO-2008049516 A3 6/2008  
 WO WO-2008152444 A2 12/2008  
 WO WO-2009002542 A1 12/2008  
 WO WO-2009036311 A1 3/2009  
 WO WO-2009040818 4/2009  
 WO WO-2008152444 A3 6/2009  
 WO WO-2009069006 A2 6/2009  
 WO WO-2009098072 A2 8/2009  
 WO WO-2009098072 A3 10/2009  
 WO WO-2009133352 A2 11/2009  
 WO WO-2009069006 A3 12/2009  
 WO WO-2010033188 A2 3/2010  
 WO WO-2009133352 A3 10/2010  
 WO WO-2010146872 A1 12/2010  
 WO WO-2011000210 A1 1/2011  
 WO WO-2011073995 A2 6/2011  
 WO WO-2011073995 A3 8/2011  
 WO WO-2011120084 A1 10/2011  
 WO WO-2011128336 A1 10/2011  
 WO WO-2010033188 A3 11/2011  
 WO WO-2012009778 A2 1/2012  
 WO WO-2012024361 A1 2/2012  
 WO WO-2012055814 A1 5/2012  
 WO WO-2012055840 A1 5/2012  
 WO WO-2012065740 A1 5/2012  
 WO WO-2012098090 A1 7/2012  
 WO WO-2012116277 A1 8/2012  
 WO WO-2012118563 A2 9/2012  
 WO WO-2012120365 A1 9/2012  
 WO WO-2012127501 A2 9/2012  
 WO WO-2012156561 A1 11/2012  
 WO WO-2012156822 A1 11/2012  
 WO WO-2012158483 A2 11/2012  
 WO WO-2012166909 A1 12/2012  
 WO WO-2012170578 A1 12/2012  
 WO WO-2013011501 A1 1/2013  
 WO WO-2012009778 A3 2/2013  
 WO WO-2013025449 A1 2/2013  
 WO WO-2013028639 A1 2/2013  
 WO WO-2013035101 A1 3/2013  
 WO WO-2013044067 A1 3/2013

WO WO-2013045404 A2 4/2013  
 WO WO-2013059285 A1 4/2013  
 WO WO-2013063279 A1 5/2013  
 WO WO-2013064620 A1 5/2013  
 WO WO-2013071281 A1 5/2013  
 WO WO-2013078422 A2 5/2013  
 WO WO-2013088254 A1 6/2013  
 WO WO-2013102665 A1 7/2013  
 WO WO-2013106437 A1 7/2013  
 WO WO-2013113690 A1 8/2013  
 WO WO-2013124415 A1 8/2013  
 WO WO-2013127727 A1 9/2013  
 WO WO-2013127728 A1 9/2013  
 WO WO-2013144356 A1 10/2013  
 WO WO-2013149258 A2 10/2013  
 WO WO-2013158454 A2 10/2013  
 WO WO-2013170052 A1 11/2013  
 WO WO-2013178587 A1 12/2013  
 WO WO-2013181449 A1 12/2013  
 WO WO-2013192248 A1 12/2013  
 WO WO-2013192249 A1 12/2013  
 WO WO-2013192250 A1 12/2013  
 WO WO-2013192251 A1 12/2013  
 WO WO-2014001904 A1 1/2014  
 WO WO-2014004424 A1 1/2014  
 WO WO-2014009434 A1 1/2014  
 WO WO-2014018569 A1 1/2014  
 WO WO-2014018570 A1 1/2014  
 WO WO-2014018571 A2 1/2014  
 WO WO-2014018856 A1 1/2014  
 WO WO-2014018932 A2 1/2014  
 WO WO-2014031958 A1 2/2014  
 WO WO-2014041120 A1 3/2014  
 WO WO-2014052792 A1 4/2014  
 WO WO-2014056897 A1 4/2014  
 WO WO-2014066442 A2 5/2014  
 WO WO-2014074846 A1 5/2014  
 WO WO-2014076231 A1 5/2014  
 WO WO-2014076569 A2 5/2014  
 WO WO-2014081598 A1 5/2014  
 WO WO-2014086739 A1 6/2014  
 WO WO-2014093114 A1 6/2014  
 WO WO-2014104784 A1 7/2014

## OTHER PUBLICATIONS

Abbas, M.A., et al., "Regression of Endometrial Implants Treated with Vitamin D3 in a Rat Model of Endometriosis," *European Journal of Pharmacology* 715(1-3):72-75, Elsevier Science, Netherlands (2013).

Abitec Corporation Excipients for the Pharmaceutical Industry—Regulatory and Product Information, 2 pages (2013).

Advisory Action dated Jan. 29, 2007 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.

Alvarez, P., et al., "Ectopic Uterine Tissue as a Chronic Pain Generator," *Neuroscience* 225:269-282, Elsevier Science, United States (2012).

Application Note JASCO CD Spectra of Pharmaceuticals Substances Steroids, 2 pages.

Archer, D.F., et al., "Effects of Ospemifene on the Female Reproductive and Urinary Tracts : Translation From Preclinical Models into Clinical Evidence," *Menopause*, Lippincott-Raven Publishers, United States (2014).

Archer, F., et al., *Estrace® vs Premarin® for Treatment of Menopausal Symptoms: Dosage Comparison Study* 9(1):21-31, (1992).  
 Ashburn, A.D., et al., "Cardiovascular, Hepatic and Renal Lesions in Mice Receiving Cortisone, Estrone and Progesterone," *The Yale Journal of Biology and Medicine* 35:329-340, Yale Journal of Biology and Medicine, United States (1963).

Bartosova, L. and Bajgar, J., "Transdermal Drug Delivery in Vitro Using Diffusion Cells," *Current Medicinal Chemistry* 19(27):4671-4677, Bentham Science Publishers, Netherlands (2012).

Benbow, A.L. and Waddell, B.J., "Distribution and Metabolism of Maternal Progesterone in the Uterus, Placenta, and Fetus During Rat Pregnancy," *Biology of Reproduction* 52(6):1327-1333, Society for the Study of Reproduction, United States (1995).



## US 10,639,375 B2

Page 11

(56)

## References Cited

## OTHER PUBLICATIONS

- Blake, E.J., et al., "Single and Multidose Pharmacokinetic Study of a Vaginal Micronized Progesterone insert (Endometrin ) Compared with Vaginal Gel in Healthy Reproductive-Aged Female Subjects," *Fertility and Sterility* 94(4):1296-1301, Elsevier for the American Society for Reproductive Medicine, United States (2010).
- Brarred Christensson, J., et al., "Positive Patch Test Reactions to Oxidized Limonene: Exposure and Relevance," *Contact Dermatitis* 71(5):264-272, Wiley, England (2014).
- Christen, R.D., et al., "Phase I/Pharmacokinetic Study of High-Dose Progesterone and Doxorubicin," *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 11(12):2417-2426, American Society of Clinical Oncology, United States (1993).
- Christensson, J.B., et al., "Limonene Hydroperoxide Analogues Differ in Allergenic Activity," *Contact Dermatitis* 59(6):344-352, Wiley, England (2008).
- Christensson, J.B., et al., "Limonene Hydroperoxide Analogues Show Specific Patch Test Reactions," *Contact Dermatitis* 70(5):291-299, Wiley, England (2014).
- Cicinelli, E., et al., "Direct Transport of Progesterone From Vagina to Uterus," *Obstetrics and Gynecology* 95(3):403-406, Lippincott Williams & Wilkins, United States (2000).
- Corbett, S.H., et al., "Trends in Pharmacy Compounding for Women'S Health in North Carolina : Focus on Vulvodynia," *Southern Medical Journal* 107(7):433-436, Southern Medical Association, United States (2014).
- Critchley, H.O., et al., "Estrogen Receptor Beta, but Not Estrogen Receptor Alpha, Is Present in the Vascular Endothelium of the Human and Nonhuman Primate Endometrium," *The Journal of Clinical Endocrinology and Metabolism* 86(3):1370-1378, Endocrine Society, United States (2001).
- Diramio, J.A., et al., "Poly(Ethylene Glycol) Methacrylate/Dimethacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," *Masters of Science Thesis, University of Georgia, Athens, Georgia*, 131 pages (2002).
- Engelhardt, H., et al., "Conceptus influences the Distribution of Uterine Leukocytes During Early Porcine Pregnancy," *Biology of Reproduction* 66(6):1875-1880, Society for the Study of Reproduction, United States (2002).
- Ettinger, B., et al., "Comparison of Endometrial Growth Produced by Unopposed Conjugated Estrogens or by Micronized Estradiol in Postmenopausal Women," *American Journal of Obstetrics and Gynecology* 176(1 Pt1):112-117, Elsevier, United States (1997).
- Excipients for Pharmaceuticals, SASOL Olefins & Surfactants GMBH, 28 pages (2010).
- Filipsson, F., et al., "Concise International Chemical Assessment Document 5," Limonene, first draft, World Health Organization, Geneva, 36 pages (1998).
- Final Office Action dated Oct. 26, 2012 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- Flyvholm, M.A. and Menne, T., "Sensitizing Risk of butylated Hydroxytoluene Based on Exposure and Effect Data," *Contact Dermatitis* 23(5):341-345, Wiley, England (1990).
- Franklin, R.D. and Kutteh, W.H., "Characterization of Immunoglobulins and Cytokines in Human Cervical Mucus : influence of Exogenous and Endogenous Hormones," *Journal of Reproductive Immunology* 42(2):93-106, Elsevier/North-Holland Biomedical Press, Ireland (1999).
- Franz, T.J., et al., "Use of Excised Human Skin to Assess the Bioequivalence of Topical Products," *Skin Pharmacology and Physiology* 22(5):276-286, Karger, Switzerland (2009).
- Fuchs, K.O., et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," *Cutis* 71(6):481-488, Frontline Medical Communications, United States (2003).
- Furness, S., et al., "Hormone therapy in Postmenopausal Women and Risk of Endometrial Hyperplasia," *The Cochrane Database of Systematic Reviews* 8:1-204, Wiley, England (2012).
- Gafvert, E., et al., "Free Radicals in Antigen formation: Reduction of Contact Allergic Response to Hydroperoxides by Epidermal Treatment with Antioxidants," *The British Journal of Dermatology* 146(4):649-656, Blackwell Scientific Publications, England (2002).
- Gattefossé SAS, Regulatory Data Sheet, Gelot 64, 6 pages (2012).
- Gattefossé SAS, Regulatory Data Sheet, Lauroglycol 90, 5 pages (2012).
- Gattefossé, "Excipients for Safe and Effective Topical Delivery," <http://drug-dev.com/Main/Back-Issues/Transdermal-Topical-Subcutaneous-NonInvasive-Deliv-5.aspx#> (2012).
- Gattefossé SAS, Material Safety Data Sheet, Gelot 64, 8 pages 2012.
- Gillet, J.Y., et al., "induction of Amenorrhea During Hormone Replacement therapy : Optimal Micronized Progesterone Dose A Multicenter Study," *Maturitas* 19(2):103-115, Elsevier/North Holland Biomedical Press, Ireland (1994).
- Glaser, R.L., et al., "Pilot Study : Absorption and Efficacy of Multiple Hormones Delivered in a Single Cream Applied to the Mucous Membranes of the Labia and Vagina," *Gynecologic and Obstetric Investigation* 66(2):111-118, Basel, New York, Karger, Switzerland (2008).
- Golotowski, C., et al., "Comparative Evaluation of Saliva Collection Methods for Proteome Analysis," *International Journal of Clinical Chemistry* 419:42-46, Elsevier, Netherlands (2013).
- Graham, J.D. and Clarke, C.L., "Physiological Action of Progesterone in Target Tissues," *Endocrine Reviews* 18(4):502-519, Endocrine Society, United States (1997).
- Groothuis, P.G., et al., "Estrogen and the Endometrium : Lessons Learned From Gene Expression Profiling in Rodents and Human," *Human Reproduction Update* 13(4):405-417, Published for the European Society of Human Reproduction and Embryology by Oxford University Press, England (2007).
- Hamid, K.A., et al., "the Effects of Common Solubilizing Agents on the intestinal Membrane Barrier Functions and Membrane Toxicity in Rats," *International Journal of Pharmaceutics* 379(1):100-108, Amsterdam, Elsevier/North-Holland Biomedical Press, Netherlands (2009).
- Hatton, J., et al., "Safety and Efficacy of a Lipid Emulsion Containing Medium-Chain Triglycerides," *Clinical Pharmacy* 9(5):366-371, American Society of Hospital Pharmacists, United States (1990).
- He, F., et al., "Apoptotic Signaling Pathways in Uteri of Rats with Endometrial Hyperplasia induced by Ovariectomy Combined with Estrogen," *Gynecologic and Obstetric Investigation* 76(1):51-56, Karger, Switzerland (2013).
- Helmy, A., et al., "Estrogenic Effect of Soy Phytoestrogens on the Uterus of Ovariectomized Female Rats," *Clinical Pharmacology & Biopharmaceutics*, S2, 7 pages (2014).
- Hostynek, J., et al., "Predicting absorption of fragrance chemicals through human skin," *Journal of the Society of Cosmetic Chemists* 46:221-229, (1995).
- Hurn, P.D. and Macrae, I.M., "Estrogen as a Neuroprotectant in Stroke," *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism* 20(4):631-652, Nature Publishing Group, United States (2000).
- Hyder, S.M., et al., "Synthetic Estrogen 17Alpha-Ethinyl Estradiol induces Pattern of Uterine Gene Expression Similar to Endogenous Estrogen 17Beta-Estradiol," *The Journal of Pharmacology and Experimental Therapeutics* 290(2):740-747, American Society for Pharmacology and Experimental Therapeutics, United States (1999).
- Joshi, S.G., et al., "Detection and Synthesis of a Progesterone-Dependent Protein in Human Endometrium," *Journal of Reproduction and Fertility* 59(2):273-285, Portland Press, England (1980).
- Kanno J., et al., "The Oecd Program to Validate the Rat Uterotrophic Bioassay to Screen Compounds for in Vivo Estrogenic Responses : Phase 1," *Environmental Health Perspectives* 109(8):785-794, N. C. National Institute of Environmental Health Sciences., United States (2001).
- Karlberg, A.T., et al., "Air Oxidation of D-Limonene (the Citrus Solvent) Creates Potent Allergens," *Contact Dermatitis* 26(5):332-340, Wiley, England (1992).

## US 10,639,375 B2

Page 12

(56)

## References Cited

## OTHER PUBLICATIONS

- Karlberg, A.T., et al., "Influence of an Anti-Oxidant on the formation of Allergenic Compounds During Auto-Oxidation of D-Limonene," *The Annals of Occupational Hygiene* 38(2):199-207, Oxford University Press, England (1994).
- Kaunitz, A.M. "Extended Duration Use of Menopausal Hormone therapy," *Menopause* 21(6):679-681, Lippincott-Raven Publishers, United States (2014).
- Kharode, Y., et al., "The Pairing of a Selective Estrogen Receptor Modulator, Bazedoxifene, with Conjugated Estrogens as a New Paradigm for the Treatment of Menopausal Symptoms and Osteoporosis Prevention," *Endocrinology* 149(12):6084-6091, Endocrine Society, United States (2008).
- Kim, Y.W., et al., "Safety Evaluation and Risk Assessment of D-Limonene," *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 16(1):17-38, Informa Healthcare, England (2013).
- Koga, K., et al., "Enhancing Mechanism of Labrasol on intestinal Membrane Permeability of the Hydrophilic Drug Gentamicin Sulfate," *European Journal of Pharmaceutics and Biopharmaceutics : Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik E.V* 64(1):82-91, Elsevier Science, Netherlands (2006).
- Komm, B.S., et al., "Bazedoxifene Acetate : A Selective Estrogen Receptor Modulator with Improved Selectivity," *Endocrinology* 146(9):3999-4008, Endocrine Society, United States (2005).
- Kumasaka, T., et al., "Effects of Various forms of Progesterin on the Endometrium of the Estrogen-Primed , Ovariectomized Rat," *Endocrine Journal* 41(2):161-169, Japan Endocrine Society, Japan (1994).
- Kuon, R.J. and Garfield, R.E., "Actions of Progestins for the inhibition of Cervical Ripening and Uterine Contractions to Prevent Preterm Birth," *Facts, Views & Vision in Obgyn* 4(2):110-119, Flemish Society of Obstetrics & Gynaecology, Belgium (2012).
- Kuon, R.J., et al., "A Novel Optical Method to Assess Cervical Changes During Pregnancy and Use to Evaluate the Effects of Progestins on Term and Preterm Labor," *American Journal of Obstetrics and Gynecology* 205(1):82.e15-82.e20, Elsevier, United States (2011).
- Kuon, R.J., et al., "Pharmacologic Actions of Progestins to inhibit Cervical Ripening and Prevent Delivery Depend on their Properties , the Route of Administration , and the Vehicle," *American Journal of Obstetrics and Gynecology* 202(5):455.e1-455.e9, Elsevier, United States (2010).
- Lanigan, R.S. and Yamarik, T.A., "Final Report on the Safety Assessment of Bht (1)," *International Journal of Toxicology* 21(2):19-94, Sage Publications, United States (2002).
- Lopez-Belmonte, J., et al., "Comparative Uterine Effects on Ovariectomized Rats After Repeated Treatment with Different Vaginal Estrogen formulations," *Maturitas* 72(4):353-358, Elsevier/North Holland Biomedical Press, Ireland (2012).
- Lauer, A.C., et al., "Evaluation of the Hairless Rat as a Model for in Vivo Percutaneous Absorption," *Journal of Pharmaceutical Sciences* 86(1):13-18, Wiley-Liss, United States (1997).
- Leonetti, H.B., et al., "Transdermal Progesterone Cream as an Alternative Progestin in Hormone therapy," *Alternative Therapies in Health and Medicine* 11(6):36-38, InnoVision Communications, United States (2005).
- Madishetti, S.K., et al., "Development of Domperidone Bilayered Matrix Type Transdermal Patches : Physicochemical , in Vitro and Ex Vivo Characterization," *Journal of Faculty of Pharmacy* 18(3):221-229, BioMed Central, England (2010).
- Miles, R.A., et al., "Pharmacokinetics and Endometrial Tissue Levels of Progesterone After Administration by intramuscular and Vaginal Routes : A Comparative Study," *Fertility and Sterility* 62(3):485-490, Elsevier for the American Society for Reproductive Medicine, United States (1994).
- Miller, J.A., et al., "Safety and Feasibility of Topical Application of Limonene as a Massage Oil to the Breast," *Journal of Cancer Therapy* 3(5A), Scientific Research Publishing, United States (2012).
- Nilsson, U., et al., "Analysis of Contact Allergenic Compounds in Oxidized d-Limonene," *Chromatographia* 42:199-205, (1996).
- Non Final Office Action dated Dec. 12, 2011 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- Notice of Allowance dated Sep. 11, 2013 for U.S. Appl. No. 12/561,515, filed Sep. 17, 2009.
- Opinion on Diethylene glycol monoethyl ether, Scientific Committee on Consumer Products, The SCCP adopted this opinion at its 10th plenary, 27 pages (2006).
- Outterson, K. "The Drug Quality and Security Act—Mind the Gaps," *The New England Journal of Medicine* 370(2):97-99, Massachusetts Medical Society, United States (2014).
- Palamakula, A., et al., "Preparation and In Vitro Characterization of Self-Nanoemulsified Drug Delivery Systems of Coenzyme Q10 Using Chiral Essential Oil Components" *Pharmaceutical Technology* 74-88, (2004).
- Panay, N., et al., "The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy," *Menopause International: The Integrated Journal of Postreproductive Health*, published online May 23, 2013, Sage Publications. <http://min.sagepub.com/content/early/2013/05/23/1754045313489645.1>.
- Parasuraman, S., et al., "Blood Sample Collection in Small Laboratory Animals," *Journal of Pharmacology & Pharmacotherapeutics* 1(2):87-93, Medknow Publications and Media, India (2010).
- Pfaus, J.G., et al., "Selective Facilitation of Sexual Solicitation in the Female Rat by a Melanocortin Receptor Agonist," *Proceedings of the National Academy of Sciences of the United States of America* 101(27):10201-10204, National Academy of Sciences, United States (2004).
- Pickles, V.R. "Cutaneous Reactions to injection of Progesterone Solutions into the Skin," *British Medical Journal* 2(4780):373-374, British Medical Association, England (1952).
- Pinkerton, J.V. "What are the Concerns About Custom-Compounded "Bioidentical" Hormone therapy?," *Menopause* 21(12):1298-1300, Lippincott-Raven Publishers, United States (2014).
- Prausnitz, M.R. and Langer, R., "Transdermal Drug Delivery," *Nature Biotechnology* 26(11):1261-1268, Nature America Publishing, United States (2008).
- Product Safety Assessment, Diethylene Glycol Monoethyl Ether, The Dow Chemical Company Page, 5 Pages (2007).
- Provider Data Sheet, "About Dried Blood Spot Testing," ZRT Laboratory, 3 pages (2014).
- Rahn, D.D., et al., "Vaginal Estrogen for Genitourinary Syndrome of Menopause: A Systematic Review," *Obstetrics and Gynecology* 124(6):1147-1156, Lippincott Williams & Wilkins, United States (2014).
- Reisman, S.A., et al., "Topical Application of the Synthetic Triterpenoid Rta 408 Protects Mice From Radiation-induced Dermatitis," *Radiation Research* 181(5):512-520, Radiation Research Society, United States (2014).
- Ross, D., et al., "Randomized , Double-Blind , Dose-Ranging Study of the Endometrial Effects of a Vaginal Progesterone Gel in Estrogen-Treated Postmenopausal Women," *American Journal of Obstetrics and Gynecology* 177(4):937-941, Elsevier, United States (1997).
- Ruan, X. and Mueck, A.O., "Systemic Progesterone therapy—Oral, Vaginal , injections and Even Transdermal ?," *Maturitas* 79(3):248-255, Elsevier/North Holland Biomedical Press, Ireland (2014).
- Salem, H.F. "Sustained-Release Progesterone Nanosuspension Following intramuscular injection in Ovariectomized Rats," *International Journal of Nanomedicine* 10:943-954, DOVE Medical Press, New Zealand (2010).
- Santen, R.J. "Vaginal Administration of Estradiol : Effects of Dose , Preparation and Timing on Plasma Estradiol Levels," *The Journal of the International Menopause Society* :1-14, Informa Healthcare, England (2014).
- Schutte, S.C. and Taylor, R.N., "A Tissue-Engineered Human Endometrial Stroma That Responds to Cues for Secretory Differentiation , Decidualization , and Menstruation," *Fertility and Sterility* 97(4):997-1003, Elsevier for the American Society for Reproductive Medicine, United States (2012).

## US 10,639,375 B2

Page 13

(56)

## References Cited

## OTHER PUBLICATIONS

- Schweikart, K.M., et al., "Comparative Uterotrophic Effects of Endoxifen and Tamoxifen in Ovariectomized Sprague-Dawley Rats," *Toxicologic Pathology* 42(8):1188-1196, Sage Publications, United States (2014).
- Shao, R., et al., "Direct Effects of Metformin in the Endometrium : A Hypothetical Mechanism for the Treatment of Women with Pcos and Endometrial Carcinoma," *Journal of Experimental & Clinical Cancer Research* 33:41, BioMed Central, England (2014).
- Shrier, L.A., et al., "Mucosal Immunity of the Adolescent Female Genital Tract," *The Journal of Adolescent Health* 32(3):183-186, Elsevier, United States (2003).
- Siew, A. et al., "Bioavailability Enhancement with Lipid-Based Durg-Delivery Systems" *Pharmaceutical Technology* 28,30-31, (2014).
- Simon, J.A. "What If the Women'S Health initiative Had Used Transdermal Estradiol and Oral Progesterone instead?," *Menopause* 21(7):769-783, Lippincott-Raven Publishers, United States (2014).
- Smyth, H.F., et al., "A 2-Yr Study of Diethylene Glycol Monoethyl Ether in Rats," *Food and Cosmetics Toxicology* 2:641-642, Pergamon Press, England (1964).
- Stanczyk, F.Z., et al., "therapeutically Equivalent Pharmacokinetic Profile Across Three Application Sites for Ag200-15 , a Novel Low-Estrogen Dose Contraceptive Patch," *Contraception* 87(6):744-749, Elsevier, United States (2013).
- Sullivan, D.W.Jr., et al., "A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient," *Food and Chemical Toxicology* 72:40-50, Elsevier Science Ltd, England (2014).
- Sun, J. "D-Limonene : Safety and Clinical Applications," *Alternative Medicine Review* 12(3):259-264, Alternative Medicine Review, United States (2007).
- Tang, F.Y., et al., "Effect of Estrogen and Progesterone on the Development of Endometrial Hyperplasia in the Fischer Rat," *Biology of Reproduction* 31(2):399-413, Society for the Study of Reproduction, United States (1984).
- Tas, M., et al., "Comparison of Antiproliferative Effects of Metformine and Progesterone on Estrogen-induced Endometrial Hyperplasia in Rats," *Gynecological Endocrinology* 29(4):311-314, Informa Healthcare, England (2013).
- Thomas, P. "Characteristics of Membrane Progesterone Receptor Alpha (Mpralpha) and Progesterone Membrane Receptor Component 1 (Pgmrcl) and their Roles in Mediating Rapid Progesterone Actions," *Frontiers in Neuroendocrinology* 29(2):292-312, Academic Press, United States (2008).
- Tuleu, C., et al., "Comparative Bioavailability Study in Dogs of a Self-Emulsifying formulation of Progesterone Presented in a Pellet and Liquid form Compared with an Aqueous Suspension of Progesterone," *Journal of Pharmaceutical Sciences* 93(6):1495-1502, Wiley-Liss, United States (2004).
- Ueda, T., et al., "Topical and Transdermal Drug Products," *Pharmacopeial Forum* 35(3):750-764, (2009).
- Voegtline, K.M. and Granger, D.A., "Dispatches From the interface of Salivary Bioscience and Neonatal Research," *Frontiers in Endocrinology* 5:25, Frontiers Research Foundation, Switzerland (2014).
- Waddell, B.J. and Bruce, N.W., "The Metabolic Clearance of Progesterone in the Pregnant Rat : Absence of a Physiological Role for the Lung," *Biology of Reproduction* 40(6):1188-1193, Society for the Study of Reproduction, United States (1989).
- Walter, L.M., et al., "the Role of Progesterone in Endometrial Angiogenesis in Pregnant and Ovariectomised Mice," *Reproduction* 129(6):765-777, Reproduction and Fertility by BioScientifica, England (2005).
- Wren, B.G., et al., "Effect of Sequential Transdermal Progesterone Cream on Endometrium , Bleeding Pattern , and Plasma Progesterone and Salivary Progesterone Levels in Postmenopausal Women," *The Journal of the International Menopause Society* 3(3):155-160, Informa Healthcare, England (2000).
- Wu, X., et al., "Gene Expression Profiling of the Effects of Castration and Estrogen Treatment in the Rat Uterus," *Biology of Reproduction* 69(4):1308-1317, Society for the Study of Reproduction, United States (2003).
- Zava, D. "Topical Progesterone Delivery and Levels in Serum, Saliva, Capillary Blood, and Tissues" *Script*:4-5.
- Zava, D.T., et al., "Percutaneous absorption of progesterone," *Maturitas* 77:91- 92, Elsevier/North Holland Biomedical Press, Ireland (2014).
- Geelen, M.J.H., et al., "Dietary Medium-Chain Fatty Acids Raise and (n-3) Polyunsaturated Fatty Acids Lower Hepatic Triacylglycerol Synthesis in Rats," *The Journal of Nutrition* 125:2449-2456, American Institute of Nutrition, United States (1995).
- Herman, A and Herman, A.P., "Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review," *Journal of Pharmacy and Pharmacology* 67(4):473-485, Royal Pharmaceutical Society, England (2014).
- Manson, J.E., et al., "Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials," *The Journal of the American Medical Association* 310:1353-1368, American Medical Association, United States (2013).
- Notice of Allowance, dated Dec. 10, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 10 pages.
- Notice of Allowance, dated Dec. 10, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 8 pages.
- Notice of Allowance, dated Dec. 15, 2014, in U.S. Appl. No. 14/099,623, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Notice of Allowance, dated Feb. 11, 2015, in U.S. Appl. No. 14/475,864, Bernick, B.A., filed Sep. 3, 2014, 9 pages.
- Notice of Allowance, dated Feb. 13, 2015, in U.S. Appl. No. 14/475,814, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Notice of Allowance, dated Jan. 22, 2015, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 5 pages.
- Notice of Allowance, dated Jul. 14, 2014, in U.S. Appl. No. 14/099,545, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Notice of Allowance, dated Jul. 15, 2014, in U.S. Appl. No. 14/099,571, Bernick, B.A., filed Dec. 6, 2013, 11 pages.
- Notice of Allowance, dated Nov. 26, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Notice of Allowance, dated Nov. 7, 2014, in U.S. Appl. No. 14/099,582, filed Dec. 6, 2013, 14 pages.
- Office Action, dated Apr. 14, 2015, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 9 pages.
- Office Action, dated Apr. 7, 2015, in U.S. Appl. No. 14/624,051, Bernick B.A., filed Feb. 17, 2015, 10 pages.
- Office Action, dated Dec. 8, 2014, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 9 pages.
- Office Action, dated Feb. 18, 2015, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 8 pages.
- Office Action, dated Jul. 18, 2014, in U.S. Appl. No. 14/099,623, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Office Action, dated Jul. 2, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Office Action, dated Jul. 3, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 16 pages.
- Office Action, dated Jul. 30, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 12 pages.
- Office Action, dated Jun. 17, 2014, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 14 pages.
- Office Action, dated Mar. 12, 2015, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 24 pages.
- Office Action, dated Mar. 27, 2014, in U.S. Appl. No. 14/099,562, Bernick, B.A., filed Dec. 6, 2013, 8 pages.
- Office Action, dated Oct. 2, 2014, in U.S. Appl. No. 14/475,864, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Office Action, dated Oct. 1, 2014, in U.S. Appl. No. 14/475,814, Bernick, B.A., filed Sep. 3, 2014, 6 pages.
- Portman, D., et al., "One-year treatment persistence with local estrogen therapy in postmenopausal women diagnosed as having vaginal atrophy," *Menopause* 22(11): 7 pages, The North American Menopause Society, United States (2015).



## US 10,639,375 B2

Page 14

(56)

## References Cited

## OTHER PUBLICATIONS

- Rao, R. and Rao, S., "Intra Subject Variability of Progesterone 200 mg Soft Capsules in Indian Healthy Adult Postmenopausal Female Subjects under Fasting Conditions," *Journal of Bioequivalence & Bioavailability* 6(4):139-143, Open Access (2014).
- Restriction Requirement, dated Mar. 28, 2014, in U.S. Appl. No. 14/099,571, Bernick, B.A., filed Dec. 6, 2013, 7 pages.
- Restriction Requirement, dated Apr. 14, 2015, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 7 pages.
- Restriction Requirement, dated Apr. 29, 2014, in U.S. Appl. No. 14/099,582, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Dec. 5, 2014, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 7 pages.
- Restriction Requirement, dated Dec. 5, 2014, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 9 pages.
- Restriction Requirement, dated Jul. 3, 2014, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 6 pages.
- Restriction Requirement, dated Mar. 16, 2015, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 7 pages.
- Restriction Requirement, dated Mar. 20, 2014, in U.S. Appl. No. 14/099,612, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Mar. 26, 2015, in U.S. Appl. No. 14/476,040, Bernick, B.A., filed Sep. 3, 2014, 7 pages.
- Restriction Requirement, dated May 13, 2014, in U.S. Appl. No. 14/099,598, Bernick, B.A., filed Dec. 6, 2013, 9 pages.
- Restriction Requirement, dated Nov. 4, 2014, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 7 pages.
- Schindler, A.E., et al., "Classification and pharmacology of progestins," *Maturitas* 46S1:S7-S16, Elsevier Ireland Ltd., Ireland (2003).
- Sitruk-Ware, R., "Pharmacological profile of progestins," *Maturitas* 47:277-283, Elsevier Ireland Ltd., Ireland (2004).
- Stanczyk, F.Z., "All progestins are not created equal," *Science* 68:879-890, Elsevier Inc., United States (2003).
- Stanczyk, F.Z., et al., "Percutaneous administration of progesterone: blood levels and endometrial protection," *Menopause* 12(2):232-237, The North American Menopause Society, United States (2005).
- Stanczyk, F.Z., "Treatment of postmenopausal women with topical progesterone creams and gels: are they effective," *Climacteric* 17(Suppl 2):8-11, International Menopause Society, United Kingdom (2014).
- Stephenson, K., "Transdermal Progesterone: Effects on Menopausal Symptoms and on Thrombotic, Anticoagulant, and Inflammatory Factors in Postmenopausal Women," *International Journal of Pharmaceutical Compounding* 12(4):295-304, IJPC, United States (2008).
- Weintraub, A., "Women Fooled by Untested Hormones From Compounding Pharmacies," *Forbes*, accessed at <http://onforbes.com/1LIUm1V>, accessed on Feb. 23, 2015, 3 pages.
- Co-pending U.S. Appl. No. 14/671,655, Inventors Amadio, J., et al., filed Mar. 27, 2015 (Not Yet Published).
- Co-pending U.S. Appl. No. 14/671,651, Inventors Cacase, J., et al., filed Mar. 27, 2015 (Not Yet Published).
- International Search Report and Written Opinion of International Application No. PCT/US2015/023041, Korean Intellectual Property Office, Republic of Korea, dated Jun. 30, 2015, 14 pages.
- Sarpal, K., et al., "Self-Emulsifying Drug Delivery Systems: A Strategy to Improve Oral Bioavailability," *Current Research & Information on Pharmaceuticals Sciences* 11(3):42-49, NIPER, India (Jul.-Sep. 2010).
- Abdalla, A., et al., "A new self-emulsifying drug delivery system (SEDDS) for poorly soluble drugs: characterization, dissolution, in vitro digestion and incorporation into solid pellets," *Eur J Pharm Sci* 35(5):457-464, Elsevier, Netherlands (2008).
- Falconer, J.R., et al., "The Effects of Supercritical Carbon Dioxide Processing on Progesterone Dispersion Systems: A Multivariate Study," *AAPS Pharm. Sci. Tech.* 13(4): 1255-1265, Springer, USA (2012).
- Restriction Requirement, dated Feb. 6, 2013, in U.S. Appl. No. 13/684,002, Bernick, B.A., filed Nov. 21, 2012, 9 pages.
- Office Action, dated Oct. 7, 2015, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 12 pages.
- Office Action, dated Jul. 15, 2016, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 15 pages.
- Office Action, dated Apr. 21, 2017, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 13 pages.
- Office Action, dated Jul. 2, 2015, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 9 pages.
- Notice of Allowance, dated Feb. 10, 2016, in U.S. Appl. No. 13/843,428, Bernick, B.A., filed Mar. 15, 2013, 10 pages.
- Office Action, dated Oct. 26, 2015, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 10 pages.
- Office Action, dated Nov. 7, 2017, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 12 pages.
- Office Action, dated Mar. 30, 2016, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 13 pages.
- Office Action, dated Jun. 19, 2015, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 11 pages.
- Office Action, dated Mar. 23, 2017, in U.S. Appl. No. 14/106,655, Bernick, B.A., filed Dec. 13, 2013, 12 pages.
- Notice of Allowance, dated Sep. 29, 2015, in U.S. Appl. No. 14/125,554, Bernick, B.A., filed Dec. 12, 2013, 9 pages.
- Notice of Allowance, dated Aug. 4, 2015, in U.S. Appl. No. 14/136,048, Bernick, B.A., filed Dec. 20, 2013, 11 pages.
- Notice of Allowance, dated Jun. 15, 2015, in U.S. Appl. No. 14/476,040, Bernick, B.A., filed Sep. 3, 2014, 9 pages.
- Office Action, dated Jul. 20, 2016, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 12 pages.
- Office Action, dated Jun. 16, 2017, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 13 pages.
- Office Action, dated Oct. 8, 2015, in U.S. Appl. No. 14/624,051, Bernick, B.A., filed Feb. 17, 2015, 7 pages.
- Notice of Allowance, dated Feb. 1, 2016, in U.S. Appl. No. 14/624,051, Bernick, B.A., filed Feb. 17, 2015, 6 pages.
- Office Action, dated Sep. 28, 2017, in U.S. Appl. No. 15/454,898, Bernick, B.A., filed Mar. 9, 2017, 10 pages.
- Acarturk, Fusun, *Mucoadhesive Vaginal Drug Delivery Systems, Recent Patents on Drug Delivery & Formulation*, vol. 3, pp. 193-205, 2009, Bentham Science Publishers.
- Bhavnani, Bhagu R., et al., *Misconception and Concerns about Bioidentical Hormones Used for Custom-Compounded Hormone Therapy*, *J Clin Endocrin Metab.*, vol. 97(3), Mar. 2012, The Endocrine Society 2011.
- Bhavnani, Bhagu R., et al., *Structure Activity Relationships and Differential Interactions and Functional Activity of Various Equine Estrogens Mediated via Estrogen Receptors (ER) and ERa and ERB*, *Endocrinology*, Oct. 2008, vol. 149(10), pp. 4857-4870, The Endocrine Society 2008.
- Du, Joanna Y., et al., *Percutaneous progesterone delivery via cream or gel application in postmenopausal women: a randomized cross-over study of progesterone levels in serum, whole blood, saliva, and capillary blood*, *Menopause: The Journal of the North American Menopause Society*, vol. 20(11), pp. 000-000, The North American Menopause Society 2013.
- Fotherby, K., *Bioavailability of Orally Administered Sex Steroids Used in Oral Contraception and Hormone Replacement Therapy*, *Contraception*, vol. 54, pp. 59-69, Elsevier Science, Inc. 1996.
- Fuchs, Katie O., et al., *The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study*, *Pharmacology/Cosmetology*, vol. 5(1), 2006.
- Hargrove, Joel T., et al., *Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone*, *Estrogen Replacement Therapy, Obstetrics & Gynecology*, vol. 73(4), pp. 606-612, Apr. 1989, The American College of Obstetricians and Gynecologists.
- International Search Report and Written Opinion for International Application No. PCT/US2013/46442, European Patent Office, Netherlands, dated Nov. 1, 2013.
- International Search Report and Written Opinion for International Application No. PCT/US2013/46443, European Patent Office, Netherlands, dated Oct. 31, 2013.
- International Search Report and Written Opinion for International Application No. PCT/US2013/46444, European Patent Office, Netherlands, dated Oct. 31, 2013.

## US 10,639,375 B2

Page 15

(56)

## References Cited

## OTHER PUBLICATIONS

International Search Report and Written Opinion for International Application No. PCT/US2013/46445, European Patent Office, Netherlands, dated Nov. 1, 2013.

Kincl, Fred A., et al., Short Communication, Increasing Oral Bioavailability of Progesterone by Formulation, *Journal of Steroid Biochemistry*, vol. 9, pp. 83-84 Pergamon Press 1978, Great Britain. The Journal of the North American Menopause Society (NAMS), Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society, *Menopause*, vol. 20(9), pp. 888-902, The North American Menopause Society 2013.

Patel, Dipen, et al., Transdermal Drug Delivery System: A Review, *The Pharma Innovation, The Pharma Journal*, vol. 1 (4), 2012.

Sarrel, Philip M., et al., The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years, *American Journal of Public Health, Research and Practice*, pp. e1-e6, Published online ahead of print Jul. 18, 2013.

Shufelt, Chrisandra L., et al., Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study, *Menopause: The Journal of the North American Menopause Society (NAMS)*, vol. 21 (3), pp. 000-000, The North American Menopause Society 2013.

Simon, James, et al., Effective Treatment of Vaginal Atrophy With an Ultra-Low-Dose Estradiol Vaginal Tablet, *Obstetrics & Gynecology*, vol. 112(5), pp. 1053-1060, pp. 373-402, Nov. 2008.

Sitruk-Ware, Regine, et al., Oral Micronized Progesterone, *Contraception*, vol. 36(4), Oct. 1987.

Sitruk-Ware, Regine, Progesterones in hormonal replacement therapy: new molecules, risks, and benefits, *Menopause: The Journal of the North American Menopause Society (NAMS)*, vol. 9(1), pp. 6-15, The North American Menopause Society 2002.

Smith, Nicholas L., et al., Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared with Oral Conjugated Equine Estrogens, *JAMA Intern Med*, pp. e1-e7, published online Sep. 30, 2013.

Stanczyk, Frank, et al., Ethinyl estradiol and 17 $\beta$ -estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment, *Contraception*, vol. 87, pp. 706-727, Elsevier 2013.

Office Action dated Jul. 16, 2013, in U.S. Appl. No. 13/684,002, Bernick et al., filed Nov. 21, 2012.

Office Action dated Mar. 20, 2013, in U.S. Appl. No. 13/684,002, Bernick et al., filed Nov. 21, 2012.

Notice of allowance dated Dec. 6, 2013, in U.S. Appl. No. 13/684,002, Bernick et al., filed Nov. 21, 2012.

Office Action dated Feb. 18, 2014, in U.S. Appl. No. 14/099,545, Bernick et al., filed Dec. 6, 2013.

Restriction Requirement dated Feb. 20, 2014, in U.S. Appl. No. 14/099,562, Bernick et al., filed Dec. 6, 2013.

Restriction Requirement dated Mar. 5, 2014, in U.S. Appl. No. 14/099,623, Bernick et al., filed Dec. 6, 2013.

Whitehead, M. I., et al., Absorption and Metabolism of Oral Progesterone, *The British Medical Journal*, vol. 280(6217), pp. 825-827, Mar. 22, 1980, BMJ Publishing Group, JSTOR.

Wood, Charles E., et al., Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys, *Breast Cancer Res Treat*, vol. 101, pp. 125-134, published online Jul. 14, 2006, Springer Science+ Business Media B.V. 2006.

International Search Report and Written Opinion for International Application No. PCT/US2013/023309, European Patent Office, Netherlands, dated Apr. 9, 2013.

International Search Report for International Application No. PCT/US2012/66406, European Patent Office, Netherlands, dated Jan. 24, 2013.

Acarturk, "Mucoadhesive Vaginal Drug Delivery System," *Recent Patents on Drug Delivery & Formulation*, 3 (3):193-205, 2009.

Fuchs et al., "The Effects of an Estrogen and Glycolic Acid Cream on the Facial Skin of Postmenopausal Women: A Randomized Histologic Study," *Aesthetic Dermatology*, 8(1):14-19, 2006.

Panay et al., "The 2013 British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy," DOI: 1177/1754045313489645, min.sagepub.com. *Menopause International: The Integrated Journal of Postreproductive Health* 0(0):1-10, 2013.

Azeem et al., "Microemulsions as a Surrogate Carrier for Dermal Drug Delivery," *Drug Development and Industrial Pharmacy*, 35(5):525-547, 2009. Abstract Only.

Azure Pharma, Inc., "ELESTRIWM—Estradiol Gel" Drug Info, <http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archived=11885>, 26 pages, 2009.

Chun et al., "Transdermal Delivery of Estradiol and Norethindrone Acetate: Effect of Vehicles and Pressure Sensitive Adhesive Matrix," *J. Kor. Pharm. Sci.*, 35(3):173-177, 2005.

Committee of Obstetric Practice, Committee Opinion—No. 522, *Obstetrics & Gynecology*, 119(4):879-882, 2012.

Diramio, "Polyethylene Glycol Methacrylate/Dimetacrylate Hydrogels for Controlled Release of Hydrophobic Drugs," The University of Georgia-Masters of Science Thesis, 131 pages, 2004. [http://athenaum.lib.uga.edu/bitstream/handle/10724/7820/diramio\\_jackie\\_a\\_200412\\_ms.pdf?sequence=1](http://athenaum.lib.uga.edu/bitstream/handle/10724/7820/diramio_jackie_a_200412_ms.pdf?sequence=1).

Ganem-Quintanar et al., "Evaluation of the transepidermal permeation of diethylene glycol monoethyl ether and skin water loss," *International Journal of Pharmaceutics*, 147(2):165-171, 1997. Abstract Only.

Johanson, "Toxicity Review of Ethylene Glycol Monomethyl Ether and its Acetate Ester," *Critical Reviews in Toxicology*, 30(3):307-345, 2000. Abstract Only.

Knuth et al., "Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations," *Advanced Drug Delivery Reviews*, 11(1-2):137-167, 1993. Abstract Only.

Lucy et al., "Gonadotropin-releasing hormone at estrus: luteinizing hormone, estradiol, and progesterone during the periestrual and postinsemination periods in dairy cattle," *Bio Reprod.*, 35(2):300-11, 1986. Abstract Only.

NuGen, "What is NuGen HP Hair Growth System?" <http://www.skinenergizer.com/Nugen-HP-Hair-Growth-System-p/senusystem.htm>, 3 pages, undated.

NuGest 900™, <http://www.lhehormoneshop.net/nugest900.htm>, 4 pages, undated.

Panchagnula et al., "Development and evaluation of an intracutaneous depot formulation of corticosteroids using Transcutol as a cosolvent: in-vitro, ex-vivo and in-vivo rat studies," *J Pharm Pharmacol*, 43(9):609-14, 1991. Abstract Only.

Sal Ole, "The physiochemical properties of oestradiol," *Journal of Pharmaceutical & Biomedical Analysis*, 5(7):635-648, 1987.

Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," *Pharmaceutical Research*, 21(2):201-230, 2004.

Tahitian Noni, "Body Balance Cream," [http://products.lni.com/dominican\\_republic/sa\\_spanish/nonistore/product/3438/3416/](http://products.lni.com/dominican_republic/sa_spanish/nonistore/product/3438/3416/), 1 page, undated.

Trommer et al., "Overcoming the Stratum Corneum: The Modulation of Skin Penetration," *Skin Pharmacol Physiol.*, 19:106-121, 2006. [http://www.nanobiotec.iqm.unicamp.br/download/Trommer\\_skin%20penetration-2006rev.pdf](http://www.nanobiotec.iqm.unicamp.br/download/Trommer_skin%20penetration-2006rev.pdf).

Agog, McKinlay, et al., Practice Bulletin, Clinical Management Guidelines for Obstetrician-Gynecologists, AGOG, No. 141, vol. 123, No. 1, Jan. 2014, *Obstetrics & Gynecology*.

Araya-Sibaja, Andrea Manela, et al., Chemical Properties of Progesterone Selected Refer., Sci Finder, 2014, American Chemical Society & US Natl. Lib. of Med.

Araya-Sibaja, Andrea M.A., Morphology Study of Progesterone Polymorphs Prepared by Polymer-Induced Heteronucleation (PIHN), *Scanning* vol. 35 pp. 213-221, 2013, Wiley Period., Inc.

Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone, SciFinder, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.

Araya-Sibaja, Andrea Manela, et al., Polymorphism in Progesterone Selected References, SciFinder, Feb. 24, 2014, pp. 1-12, American Chem. Society & Natl. Lib. of Med.



## US 10,639,375 B2

Page 16

(56)

## References Cited

## OTHER PUBLICATIONS

- Bakhmutova-Albert, Ekaterina, et al., Enhancing Aqueous Dissolution Rates of Progesterone via Cocrystallization, SSCI, Division of Aptuit, Poster No. R6247, West Lafayette.
- Banerjee, Sila, et al., On the Stability of Salivary Progesterone Under Various Conditions of Storage, *Steroids*, vol. 46(6), pp. 967-974, Dec. 1985.
- Barnett, Steven M., Pressure-tuning infrared and solution Raman spectroscopic studies of 17B-estradiol and several A-ring . . . , *Vibrational Spectroscopy* 8, Elsevier, pp. 263, 1995.
- Bernabei, M.T., et al., Release of progesterone polymorphs from dimethylpolysiloxane polymeric matrixes, *Bollettino Chimico Farmaceutico*, vol. 122(1) pp. 20-26, 1983 SciFinder.
- Bhavnani, B.R., Stanczyk, F.Z., Pharmacology of conjugated equine estrogens: Efficacy, safety and mechanism of action, *J. Steroid Biochem. Mol. Bioi.* (2013), Elsevier.
- Bhavnani, B.R., Stanczyk, F.Z., Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe? *J. Steroid Biochem. Mol. Bioi.* (2013), Elsevier.
- BioMed Central, Solubility of Progesterone in Organic Solvents, Online PDF, <http://www.biomedcentral.com/content/supplementary/1475-2859-11-1-06-S2.pdf>.
- Borka, Laszlo, Crystal Polymorphism of Pharmaceuticals, *Acta Pharm. Jugosl.*, vol. 40 pp. 71-94, 1990.
- Brandstatter-Kuhnert, M., Zur mikroskopischen Identitätsprüfung und zur Polymorphie der Sexualhormone, *Acta*, vol. 16, pp. 847-853, 1959, Univ. Innsbruck.
- Brinton, L.A., Felix, A.S., Menopausal hormone therapy and risk of endometrial cancer, *J. Steroid Biochem. Mol. Bioi.* (2013), Elsevier.
- Burry, Kenneth A., Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen, *Am J Obstet Gynecol*, vol. 180(6) part 1, pp. 1504-1511, 1999.
- Busetta, Par Bernard, Structure Cristalline et Moléculaire de l'Oestradiol Hemihydrate, *Acta Cryst.*, B28 pp. 560, 1972, Bis( dimethyl-o-thiophenylarsine)palladium(II).
- Busetta, Par Bernard, Structure Cristalline et Moléculaire du Complexe Oestradiol-Propanol, *Acta Cryst.*, B28 pp. 1349, 1972, J.A. Kanthers and J. Kroon.
- Campsteyn, Par H, et al., Structure Cristalline et Moléculaire de la Progesterone C21 H3002, *Acta Cryst.*, B28 pp. 3032-3042, 1972.
- Cendejas-Santana, G, et al., Growth and characterization of progesterone crystallites, *Revista Mexicana de Fisica*, 50, Suplemento 1 pp. 1-3, 2004.
- Cole, Wayne & Julian, Percy L, Sterols. I. A Study of the 22-Ketosteroids, Cont. of the Research Lab. of the Glidden Co., Soya Prod. Div., vol. 67 pp. 1369-1375, Aug. 1945, Chicago.
- Commodari, Fernando, Comparison of 17B-estradiol structures from x-ray diffraction and solution NMR, *Magn. Reson. Chem.*, vol. 43, pp. 444-450, 2005, Wiley InterScience.
- Cooper, A, et al., Systemic absorption of progesterone from Progest cream in postmenopausal women, *The Lancet*, vol. 351, pp. 1255-1256, Research Letters, Apr. 25, 1998.
- Dideberg, O, et al., Crystal data on progesterone (C21 H3002), desoxycorticosterone (C21 H3003), corticosterone (C21 H3004) and aldosterone . . . , *J. Appl. Cryst.* vol. 4 pp. 80, 1971.
- Drakulic, Branko J, Role of complexes formation between drugs and penetration enhancers in transdermal . . . , *Inter. Journal of Pharmaceutics*, Elsevier, vol. 363, pp. 40-49, 2009.
- Duax, William L, et al., Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations, *J. Am. Chem. Soc.*, vol. 103 pp. 6705-6712, Jun. 1981.
- Duclos, R, et al., Polymorphism of Progesterone: Influence of the carrier and of the solid dispersion manufacturing . . . , *J. Thermal Anal.*, vol. 37 pp. 1869-1875, 1991, Wiley.
- Ebian, A.R., Ebian Article: Polymorphism and solvation of ethinyl estradiol, *Sci Finder, Pharmaceutica Acta Helveticae*, vol. 54(4), pp. 111-114, 1979, Alexandria, Egypt.
- Eisenberger, A., Westhoff, C., Hormone replacement therapy and venous thromboembolism, *J. Steroid Biochem. Mol. Bioi.* (2013), Elsevier.
- Faassen, Fried, Physicochemical Properties and Transport of Steroids across Caco-2 Cells, *Pharmaceutical Research*, vol. 20(2), 2003, Plenum Pub. Corp.
- FDA, Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb. 2011 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf>.
- Freedman, R. R., Menopausal hot flashes: Mechanisms, endocrinology, treatment, *J. Steroid Biochem. Mol. Bioi.* (2013), Elsevier.
- Fugh-Berman, Adriane, Bioidentical Hormones for Menopausal Hormone Therapy: Variation on a Theme, *Journal of General Internal Medicine*, vol. 22, pp. 1030-1034, 2007.
- Giron, D, Thermal analysis and calorimetric methods in the characterization of polymorphs and solvates, *Thermochimica Acta*, vol. 248 pp. 1-59, 1995, Elsevier.
- Giron-Forest, D, et al., Thermal analysis methods for pharmacopoeial materials, *J. Pharmaceutical & Biomedical Anal.*, vol. 7(12) pp. 1421-1433, 1989, Pergamon Press, Gr. Britain.
- Gurney, E.P., et al., The Women's Health Initiative trial and related studies: 10 years later: A clinician's view, *J. Steroid Biochem. Mol. Bioi.* (2013), Elsevier.
- Haner, Barbara A., Crystal data (I) for some pregnenes and pregnadienes, *Acta Cryst.*, vol. 17 pp. 1610, 1964.
- Hapgood, J.P., et al., Potency of progestogens used in hormonal therapy: Toward understanding differential actions, *J. Steroid Biochem. Mol. Bioi.* (2013), Elsevier.
- Helbling, Ignacio M, et al., The Optimization of an Intravaginal Ring Releasing Progesterone Using a Mathematical Model, *Pharm Res*, vol. 31 pp. 795-808, 2014, Springer Science.
- Henderson, V.W., Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after . . . , *J. Steroid Biochem. Mol. Bioi.* (2013), Elsevier.
- Henriksen, Thormod, et al., An ENDOR Study of Radiation-Induced Molecular Damage to Progesterone, *Jour. of Mag. Resonance*, vol. 63, pp. 333-342, 1985, Academic Press, Inc.
- Hodis, H.N., Mack, W.J., Hormone replacement therapy and the association with heart disease and overall mortality: Clinical . . . , *J. Steroid Biochem. Mol. Bioi.* (2013), Elsevier.
- Hospital, Michel, et al., X-ray Crystallography of Estrogens and Their Binding to Receptor Sites, *Mol. Pharmacology*, vol. 8 pp. 438-445, Academic Press, Inc., 1972.
- Hulsmann, Stefan, Stability of Extruded 17B-Estradiol Solid Dispersions, *Pharmaceutical Development and Tech.*, vol. 6(2) pp. 223-229, 2001, Marcel Dekker, Inc.
- Ioder, Salima, et al., Physicochemical properties of Progesterone, *Sci Finder*, pp. 1-26, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Johnson, Williams, et al., Racemic Progesterone, *Tetrahedron Letters* No. 4, pp. 193-196, 1963, Pergamon Press Ltd., Great Britain.
- Khalil, Sah, Stability and Dissolution Rates of Corticosteroids in Polyethylene Glycol Solid Dispersions, *Drug Dev. & Indus. Pharm.*, vol. 10(5) pp. 771-787, 1984, Marcel Dekker.
- Korkmaz, Filiz, Biophysical Studies of Progesterone-Model Membrane Interactions, Thesis, Grad. School of Nat. and App. Sci. of the Middle East Tech. University, Sep. 2003.
- Kotiyani, P.N., Stability indicating HPTLC method for the estimation of estradiol, *Journal of Pharmaceutical and Biomedical Analysis*, vol. 22 pp. 667-671, 2000, Elsevier.
- Krzyminiewski, R, et al., EPR Study of the Stable Radical in a y-Irradiated Single Crystal of Progesterone, *Jour. of Mag. Resonance*, vol. 46 pp. 300-305, 1982, Academic Press.
- Stanczyk, F.Z., Bhavnani, B.R., Current views of hormone therapy for the management and treatment of postmenopausal women, *J. Steroid Biochem. Mol. Bioi.* (2014), Elsevier.
- Stein, Emily A, et al., Progesterone Physical Properties, *Sci Finder*, pp. 1-46, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Stein, Emily A, et al., Progesterone Physical Properties, *Sci Finder*, pp. 1-46, Mar. 3, 2014, American Chem. Society & US Natl. Lib. of Med.

## US 10,639,375 B2

Page 17

(56)

## References Cited

## OTHER PUBLICATIONS

- Stein, Emily A, et al., Progesterone, Sci Finder Scholar Search, pp. 1-46, Feb. 24, 2014, American Chem. Society & Natl. Lib. of Med.
- Struhar, M, et al., Estradiol Benzoate: Preparation of an injection suspension . . . , SciFinder, Cesko-Slovenska Farmacie, vol. 27(6), pp. 245-249, 1978, Bratislava, Czech.
- Tait, Alex D, Characterization of the Prod. from the Oxidation of Progesterone with Osmium Tetroxide, Dept of Investigative Med., Univ. Cambridge, Gt. Britain pp. 531-542, 1972.
- Takacs M, et al., The light sensitivity of corticosteroids in crystalline form, Pharmaceutica acta Helvetica, vol. 66 (5-6) pp. 137-140, 1991, Hardin Library.
- Tan, Melvin S, et al., A Sensitive Method for the Determination of Progesterone in Human Plasma by LC-MS-MS, M1025, Cedra Corporation, Austin, Texas.
- Tella, S.H., Gallagher, J.C., Prevention and treatment of postmenopausal osteoporosis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Thomas, Joshua, et al., The effect of water solubility of solutes on their flux through human skin in vitro: An . . . , Inti. J. of Pharmaceut., vol. 339 pp. 157-167, 2007, Elsevier.
- Tripathi, R, et al., Study of Polymorphs of Progesterone by Novel Melt Sonocrystallization Technique: A Technical Note, AAPS PhamSciTech, vol. 11, No. 3, Sep. 2010.
- USP Monographs: Progesterone. USP29, [www.pharmacopeia.cn/v29240/usp29nf24sO\\_m69870.html](http://www.pharmacopeia.cn/v29240/usp29nf24sO_m69870.html), search done: Feb. 25, 2014.
- Utian, Wulf H, et al., Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens . . . Fertility and Sterility, vol. 75(6) pp. 1065, Jun. 2001.
- Weber, M.T., et al., Cognition and mood in perimenopause: A systematic review and meta-analysis, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Wiranidchapong, Chutima, Method of preparation does not affect the miscibility between steroid hormone and polymethacrylate, Thermochimica Acta 485, Elsevier, pp. 57, 2009.
- Yalkowsky, Samuel H, & Valvani, Shri C, Solubility and Partitioning 1: Solubility of Nonelectrolytes in Water, J. of Pharmaceutical Sciences, vol. 69(8) pp. 912-922, 1980.
- Yalkowsky, Samuel H, Handbook of Aqueous Solubility Data, Solutions, pp. 1110-1111, CRC Press, Boca Raton, London, New York, Wash. D.C.
- Yue, W., Genotoxic metabolites of estradiol in breast: potential mechanism of estradiol induced carcinogenesis, 18 Journal of Steroid Biochem & Mol Biology, vol. 86 pp. 477-486, 2003.
- Kubli-Garfias, C, et al., Ab initio calculations of the electronic structure of glucocorticoids, Jour. of Mol. Structure, Theochem, vol. 454 pp. 267-275, 1998, Elsevier.
- Kubli-Garfias, Carlos, Ab initio study of the electronic structure of progesterone and related progestins, Jour. of Mol. Structure, Theochem vol. 425, pp. 171-179, 1998, Elsevier.
- Kuhnert-Brandstaetter, M & Kofler, A, Zur Unterscheidung von losungsmittelhaltigen pseudopolymorphen Kristallformen und polymorphen Modifikationen bei Steroidhormonen. II. vol. 1 pp. 127-139, 1968, Mikrochimica Acta.
- Kuhnert-Brandstaetter, M & Linder, R, Zur Hydratbildung bei Steroidhormonen, Sci. Ph arm., vol. 41 (2) pp. 109-116, 1973.
- Kuhnert-Brandstaetter, M, Thermo-microscopic and spectrophotometric: Determination of steroid hormones, Microchemical Journal 9, pp. 105-133, 1965.
- Labrie, et al., Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens, Journal of Steroid Biochemistry & Molecular Biology, vol. 138, pp. 359-367, 2013, Elsevier.
- Lacey, J.V. Jr., The WHI ten year's later: An epidemiologist's view, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Lahiani-Skiba, Malika, Solubility and Dissolution Rate of Progesterone-Cyclodextrin . . . , Drug Development and Industrial Pharmacy, Informa Healthcare vol. 32, pp. 1043-1058, 2006.
- Lancaster, Robert W, et al., The Polymorphism of Progesterone: Stabilization of a 'Disappearing' Polymorph by . . . , Jour. of Pharm. Sci., vol. 96(12) pp. 3419-3431, 2007, Wiley-Liss.
- Land, Laura M, The influence of water content of triglyceride oils on the solubility of steroids, Pharmaceutical Research, vol. 22(5) May 2005, Springer Science+Business Media.
- Leonetti, Helene B, et al., Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium, Fertility and Sterility, vol. 79(1) Jan. 2003.
- Lewis, John G., et al., Caution on the use of saliva measurements to monitor absorption of progesterone . . . , Maturitas, The European Menopaus Journal, vol. 41, pp. 1-6, 2002.
- Li, Guo-Chian, Solid-state NMR analysis of steroidal conformation of 17a- and 17B-estradiol in the absence and presence of lipi . . . , Steroids, Elsevier, vol. 177, pp. 185-192, 2012.
- Lobo, R.A., Foreword, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Lvova, M. SH., et al., Thermal Analysis in the Quality Control and Standardization of Some Drugs, J Thermal Anal., 15 vol. 40 pp. 405-411, 1993, Wiley.
- Magness, R.R., et al., Estrone, Estradiol-17b and Progesterone Concentrations in Uterine Lymph and Systemic Blood . . . , Journal of Animal Science, vol. 57, pp. 449-455, ISU, 1983.
- McGuffy, Irena, Softgel Technology as a Lipid-Based Delivery Tool for Bioavailability Enhancement, Catalent Pharma Solutions, Somerset, NJ, Mar. 2011.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 17, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index Online, Progesterone, Royal Society of Chemistry, 2013, search Feb. 24, 2014 <https://www.rsc.org/Merck-Index/monograph/print/mono1500007889/progesterone?q=authorize>.
- Merck Index, Estradiol, The Merck Index Online, Royal Society of Chemistry 2014, MON01500003758.
- Mesley, R.J., Clathrate Formation from Steroids, Chemistry and Industry, vol. 37 pp. 1594-1595, Sep. 1965.
- Miao, Wen Bin, et al., Chemical Properties of Progesterone, Sci Finder, 2014, American Chemical Society & US Natl. Lib. of Med.
- Mueck, A.O., et al., Genomic and non-genomic actions of progestogens in the breast, J. Steroid Biochem. Mol. Biol. (2013), Elsevier.
- Muramatsu, Mitsuo, Thermodynamic Relationship between a- and B- Forms of Crystalline Progesterone, J. Pharmaceutical Sciences, vol. 68(2) pp. 175-178, 1979, Amer. Pharm. Assoc.
- Nicklas, Martina, Preparation and characterization of marine sponge collagen nanoparticles and employment for the trans . . . , Drug Devel. & Indust. Pharmacy, 35(9) pp. 1035, 2009.
- O'Leary, Peter, Salivary, but not serum or urinary levels of progesterone are elevated after topical . . . , Clinical Endocrinology, vol. 53 pp. 615-620, Blackwell Science 2000.
- Open Notebook, Science Solubility Challenge, Jul. 16, 2013, Solubility of progesterone in organic solvents, <http://Ixsr7.ou.edu/-alang/onsc/solubility/allsolvents.php?solute=progesterone>.
- Park, Jeong-Sook, Solvent effects on physicochemical behavior of estradiols recrystallized for transdermal delivery, Arch Pharm Res, vol. 31(1), pp. 111-116, 2008.
- Park, Jeong-Sook, Use of CP/MAS solid-state NMR for the characterization of solvate . . . , European Journal of Pharmaceutics and Biopharmaceutics, vol. 60, pp. 407-412, 2005.
- Parrish, Damon A., A new estra-1,3,5(10)-triene-3, 17b-diol solvate: estradiol-methanol-water, Crystal Structure Comm., Intn'l Union of Crystallography, ISSN 0108-2701, 2003.
- Payne, R.S., et al., Examples of successful crystal structure prediction: polymorphs of primidone and progesterone, Inti. Jour. of Pharma., vol. 177 pp. 231-245, 1999, Elsevier.
- Persson, Linda C, et al., Physicochemical Properties of Progesterone Selecte, Sci Finder, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Pheasant, Richard, Polymorphism of 17-Ethinylestradiol, Schering Corporation, Bloomfield, NJ, May 1950.
- Pinkerton, J.V., Thomas, S., Use of SERMs for treatment in postmenopausal women, J. Steroid Biochem. Mol. Biol. (2014), Elsevier.
- Pisegna, Gisela L, A High-pressure Vibrational Spectroscopic Study of Polymorphism in Steroids . . . , Thesis, McGill University, Dept. of Chem, Nov. 1999, Natl. Lib. of Canada.

## US 10,639,375 B2

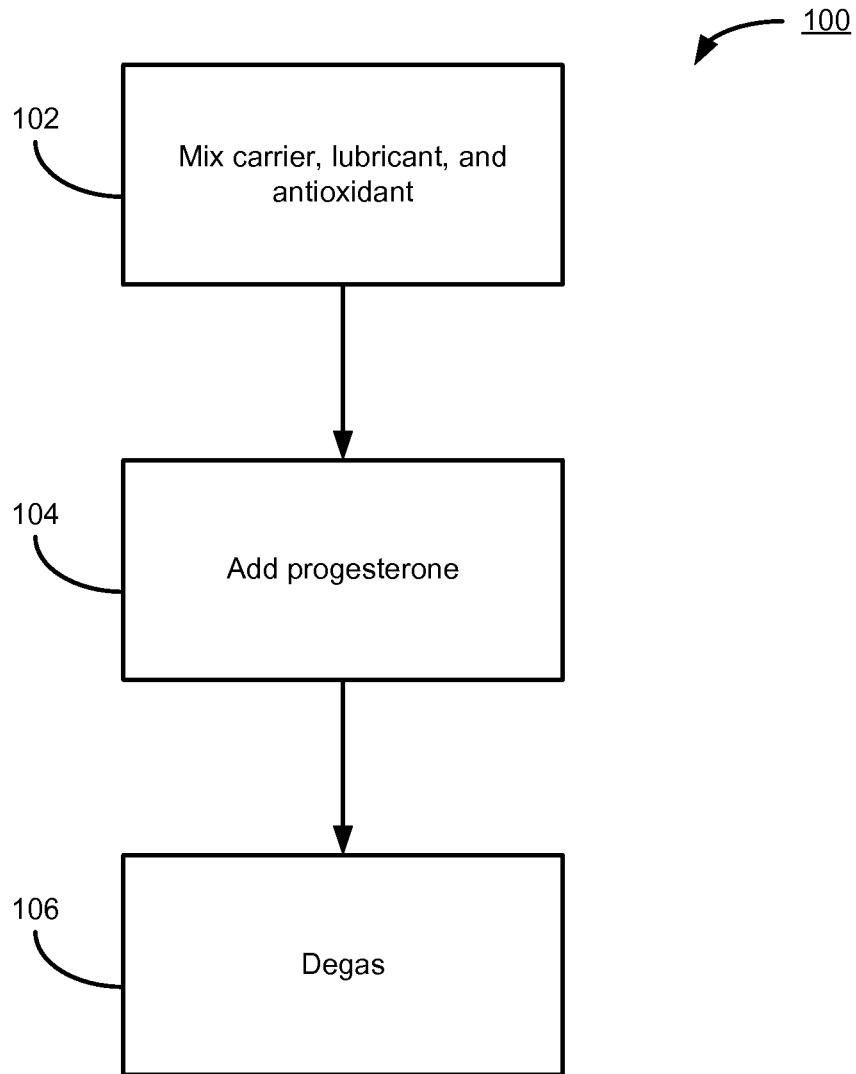
Page 18

(56)

## References Cited

## OTHER PUBLICATIONS

- Price, Sarah L., The computational prediction of pharmaceutical crystal structures and polymorphism, *Adv. Drug Delivery Reviews*, vol. 56 pp. 301-319, 2004, Elsevier.
- Progynova TS 100, available online at file:///C:/Users/Caii%20Family/Desktop/Progynova%20TS%20100%2012%20Patches\_Pack%20%28Estradiol%20Hemihydrate%29.html, 2010.
- Rosilio, V, et al., Physical Aging of Progesterone-Loaded Poly{D,L-lactide-co-glycolide} Microspheres, *Pharmaceutical Research*, vol. 15(5) pp. 794-799, 1998, Plenum Pub. Corp.
- Sal Ole, Eugene G., Estradiol, *Analytical Profiles of Drug Substances*, vol. 15, pp. 283-318, 1986.
- Santen, R.J., Menopausal hormone therapy and breast cancer, *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Sarkar, Basu, et al., Chemical Stability of Progesterone in Compounded Topical Preparations using PLO Transdermal Cream<sup>TM</sup> and HRT Cream<sup>TM</sup> Base . . . , *J Steroids Horm Sci*, 4:2, 2013.
- Satyanarayana, D, et al., Aqueous Solubility Predictions of Aliphatic Alcohols, Alkyl Substituted Benzoates and Steroids, *Asian J. Chem.*, vol. 9 (3) pp. 418-426, 1997.
- Scavarelli, Rosa Maria, et al., Progesterone and Hydrate or Solvate, *Sci Finder*, pp. 1-2, Feb. 24, 2014, American Chem. Society.
- Schindler, A. E., The "newer" progestogens and postmenopausal hormone therapy (HRT), *J. Steroid Biochem. Mol. Biol.* (2013), Elsevier.
- Sci Finder Scholar Prednisone Chemical Properties, *Sci Finder*, 2014, pp. 1-7, National Library of Medicine.
- Sci Finder Scholar Prednisone Physical Properties, *Sci Finder*, 2014, pp. 1-10, National Library of Medicine.
- SciFinder Scholar Progesterone Experimental Properties, *SciFinder*, pp. 1-9, Feb. 24, 2014, American Chem. Society.
- Serantoni, Foresti, et al., 4-Pregnen-3,20-dione (progesterone, form II), *Crystal Structure Comm.*, vol. 4(1) pp. 189-192, 1975, CAPLUS Database.
- Sharma, H. C., et al., Physical Properties of Progesterone Selected Refer, *Sci Finder*, pp. 1-5, Feb. 24, 2014, American Chem. Society & US Natl. Lib. of Med.
- Sigma-Aldrich, Progesterone-Water Soluble: powder, BioReagent, suitable for cell culture), MSDS available online: <http://www.sigmaaldrich.com/catalog/product/sigma/p7556>.
- Abitec, CapmuiMCM, EP, Technical Data Sheet, version 10, 2014, Columbus, OH.
- Abitec, CapmuiMCM, NF, Technical Data Sheet, version 6, 2014, Columbus, OH.
- Abitec, CapmuiMCM, Safety Data Sheet, 2011, Janesville, WI.
- Abitec, CapmuiMCM, Technical Data Sheet, version 17, 2014, Columbus, OH.
- Abitec, CapmuiPG8, CAS No. 31565-12-5, version 11, 2006, Columbus, OH.
- Alabi, K. A., et al., Analysis of Fatty Acid Composition of Thevetia peruviana and Hura crepitans Seed oils using GC-FID, *Fountain Journal of Nat. and Appl. Sciences*, vol. 2(2), pp. 32-37, 2013, Osogbo.
- Alexander, KS, Corn Oil, CAS No. 8001-30-7, Jan. 2009.
- British Pharmacopoeia 2014 Online, Refined Maize Oil, Ph. Eur. Monograph 1342, vol. I & II, Monographs: Medicinal and Pharmaceutical Substances, <http://www.pharmacopoeia.co.uk/lbp2014/ixbin/bp.cgi?a=print&id=7400&tab=a-z%20index>[Feb. 3, 2014 1:37:50 PM].
- ChemPro, Top-Notch Technology in Production of Oils and Fats, Chempro-Edible-Oil-Refining-ISO-TUV-Austria.
- Corn Refiners Assoc. Corn Oil, 5th Edition, Washington, D.C., 2006.
- Dauqan, Eqbal M.A., et al., Fatty Acids Composition of Four Different Vegetable Oils (Red Palm Olein, Palm Olein, Corn Oil, IPCBEE, vol. 14, 2011, IACS IT Press, Singapore.
- Ferrari, Roseli AP, et al., Oxidative Stability of Biodiesel From Soybean Oil Fatty Acid Ethyl Esters, *Sci. Agric.*, vol. 62(3), pp. 291-295, 2005, Piracicaba, Braz.
- Gunstone, Frank D, et al., *Vegetable Oils in Food Technology: Composition, Properties and Uses*, Blackwell Publishing, CRC Press, 2002.
- Ng, Jo-Han, et al., Advances in biodiesel fuel for application in compression ignition engines, *Clean Techn Environ Policy*, vol. 12, pp. 459-493, 2010, Springer-Verlag.
- Notelovitz, Morris, et al., Initial 17-b-Estradiol Dose for Treating Vasomotor Symptoms, *Obstetrics & Gynecology*, vol. 95(5), pp. 726-731, part 1, May 2000, Elsevier.
- Prajapati, Hetal N, et al., A comparative Evaluation of Mono-, Di- and Triglyceride of Medium Chain Fatty Acids by Lipid/SurfactantUWater, *Springerlink.com*, pp. 1-21, Apr. 2011.
- Strocchi, Antonino, Fatty Acid Composition, and Triglyceride Structure of Corn Oil, Hydrogenated Corn Oil, and Corn Oil Margarine, *Journal of Food Science*, vol. 147, pp. 36-39, 1981.
- USP, 401 Fats and Fixed Oils, Chemical Tests, Second Supplement to USP36-NF 31, pp. 6141-6151, 2013.
- USP, Lauroyl Polyoxylglycerides, Safety Data Sheet, US, 5611 Version #02, pp. 1-9, 2013.
- USP, Official Monographs, Corn Oil, NF 31, pp. 1970-1971, Dec. 2013.
- USP, Official Monographs, Lauroyl Polyoxylglycerides, NF 31, pp. 2064-2066, Dec. 2013.
- USP, Official Monographs, Medium Chain Triglycerides, NF 31, pp. 2271-2272, Dec. 2013.
- USP, Official Monographs, Mono- and Di-glycerides, NF 31, pp. 2101, Dec. 2013.
- USP, USP Certificate-Corn Oil, Lot GOL404, Jul. 2013.
- Weber, E.J., Corn Lipids, *Cereal Chem.*, vol. 55(5), pp. 572-584, The American Assoc of Cereal Chem, Sep.-Oct. 1978.
- Araya-Sibaja, et al., Crystallization of progesterone polymorphs using polymer-induced heteronucleation (PIHn) method, *Drug Development and Industrial Pharmacy*, Early Online, pp. 1-8, 2014, Informa Healthcare.
- PCCA, Apothogram, PCCA, May 2014, Houston, TX.
- Office Action, dated Jan. 19, 2018, in U.S. Appl. No. 13/843,362, Bernick, B.A., filed Mar. 15, 2013, 13 pages.
- Office Action, dated Apr. 16, 2018, in U.S. Appl. No. 14/521,230, Bernick, B.A., filed Oct. 22, 2014, 14 pages.



**FIG. 1**

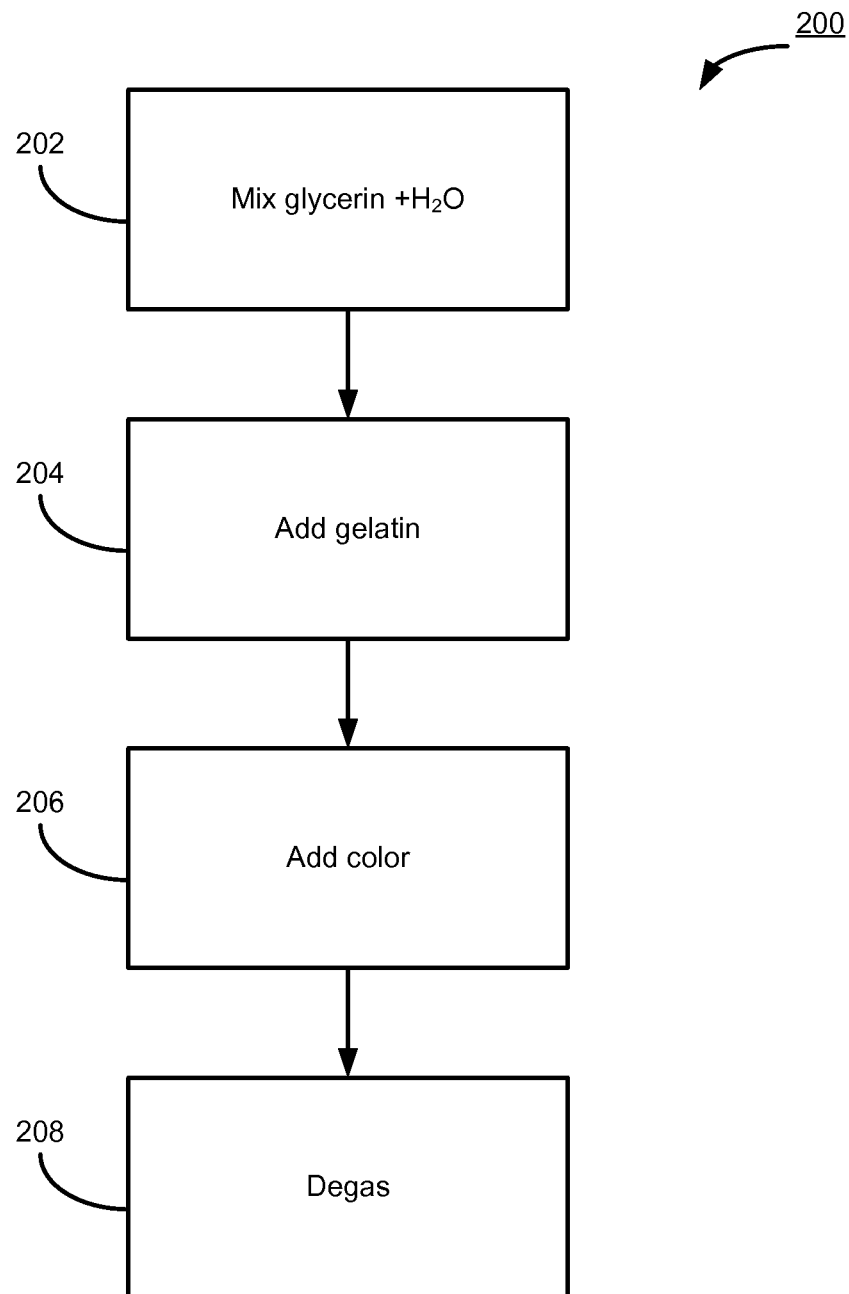


FIG. 2



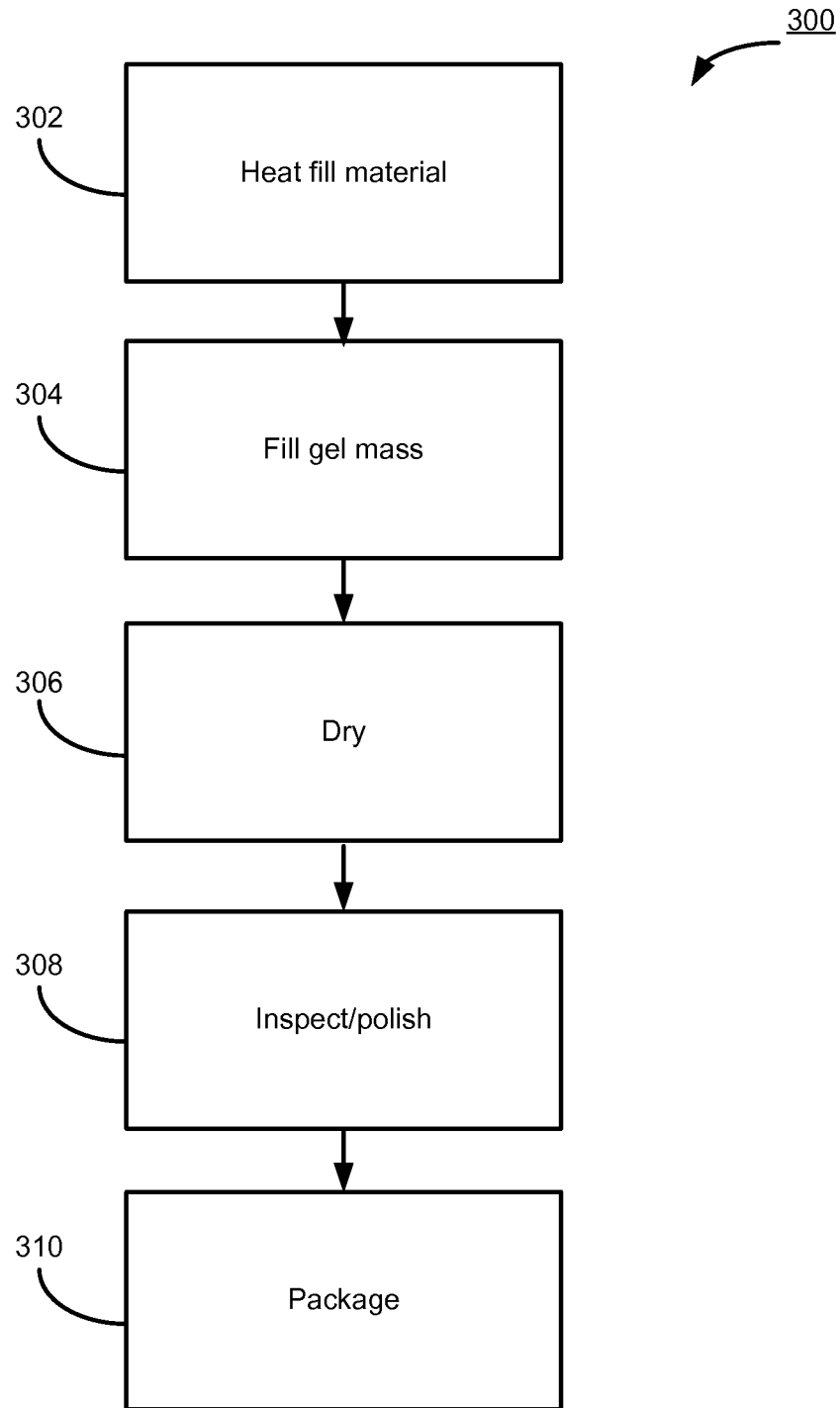


FIG. 3

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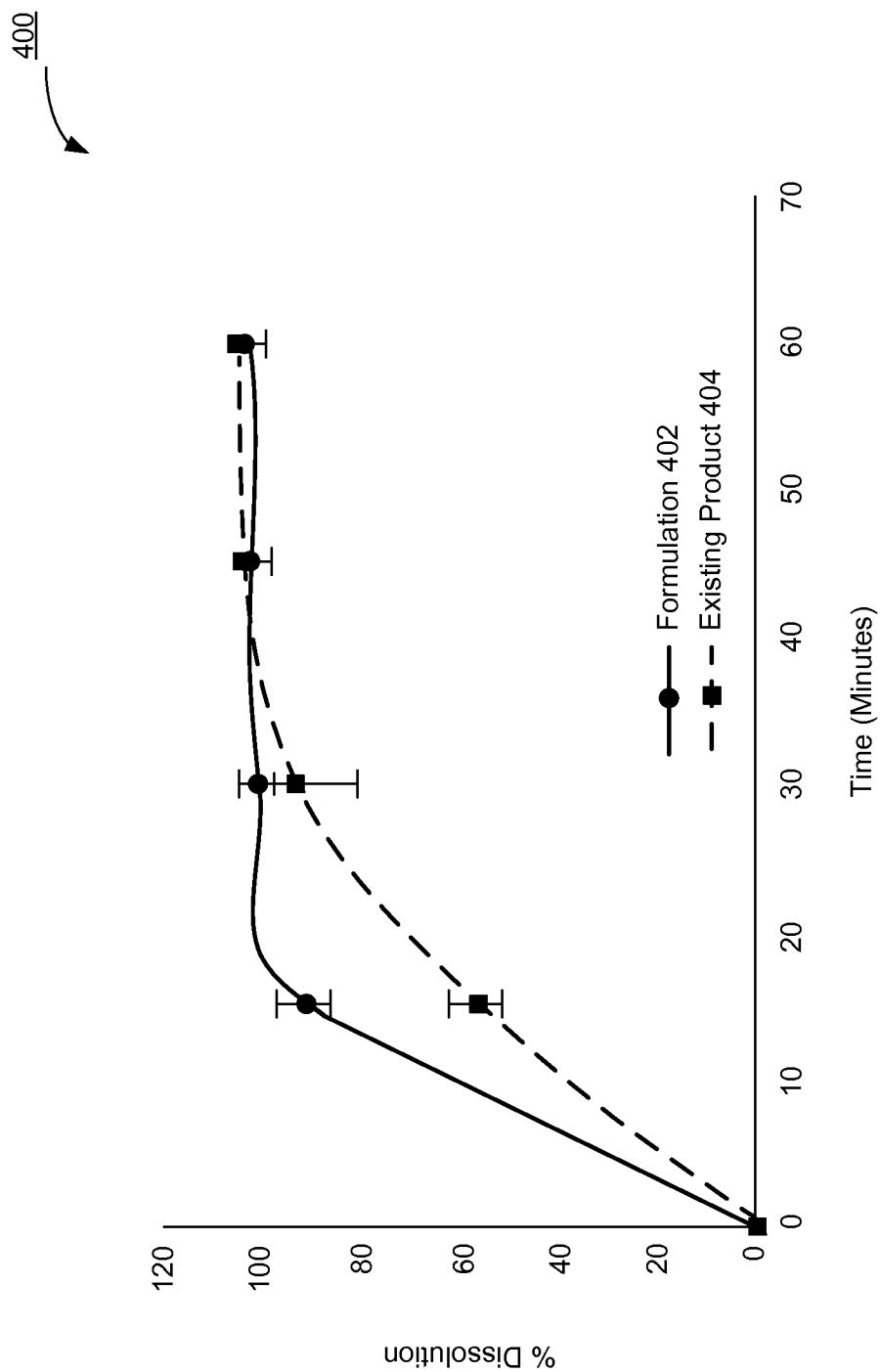


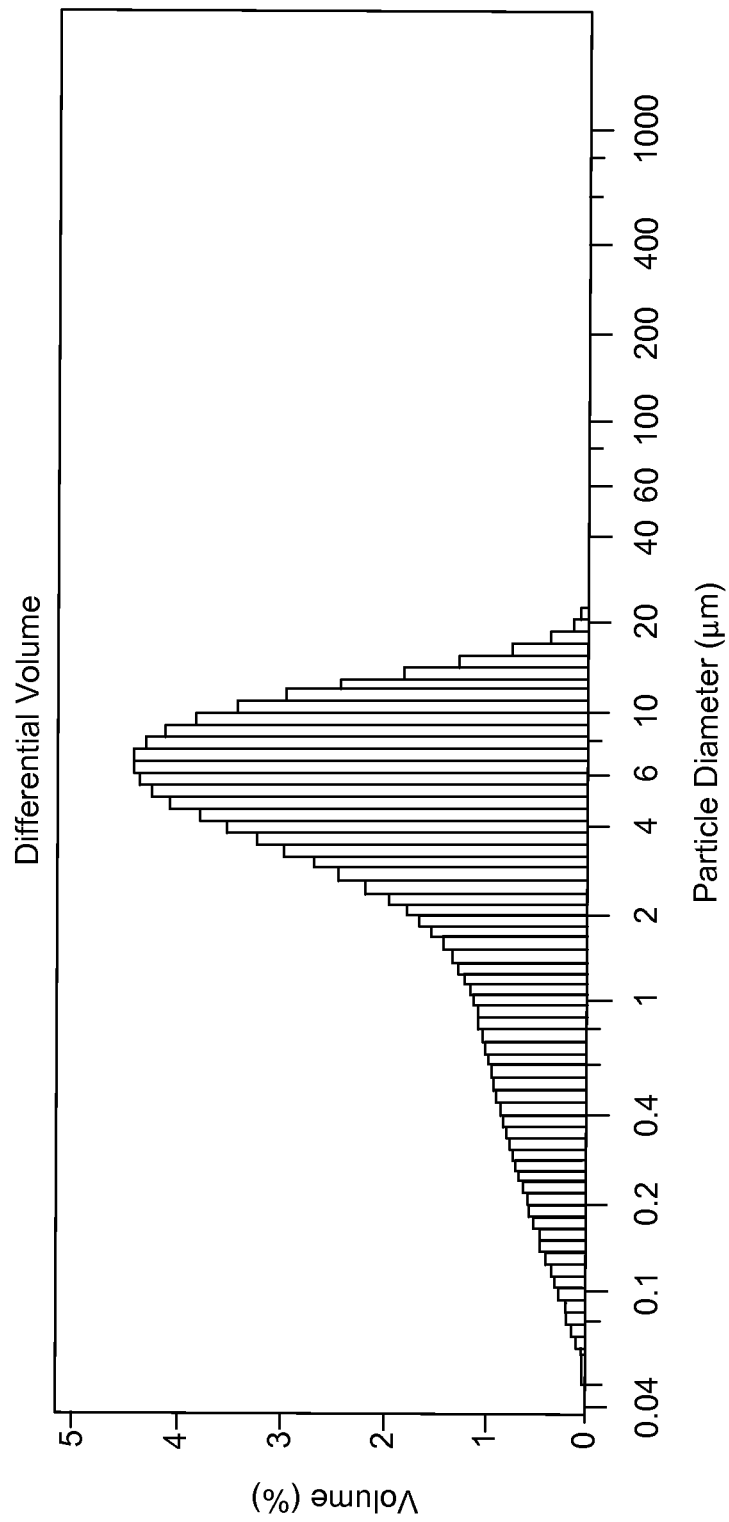
FIG. 4

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**FIG 5.**

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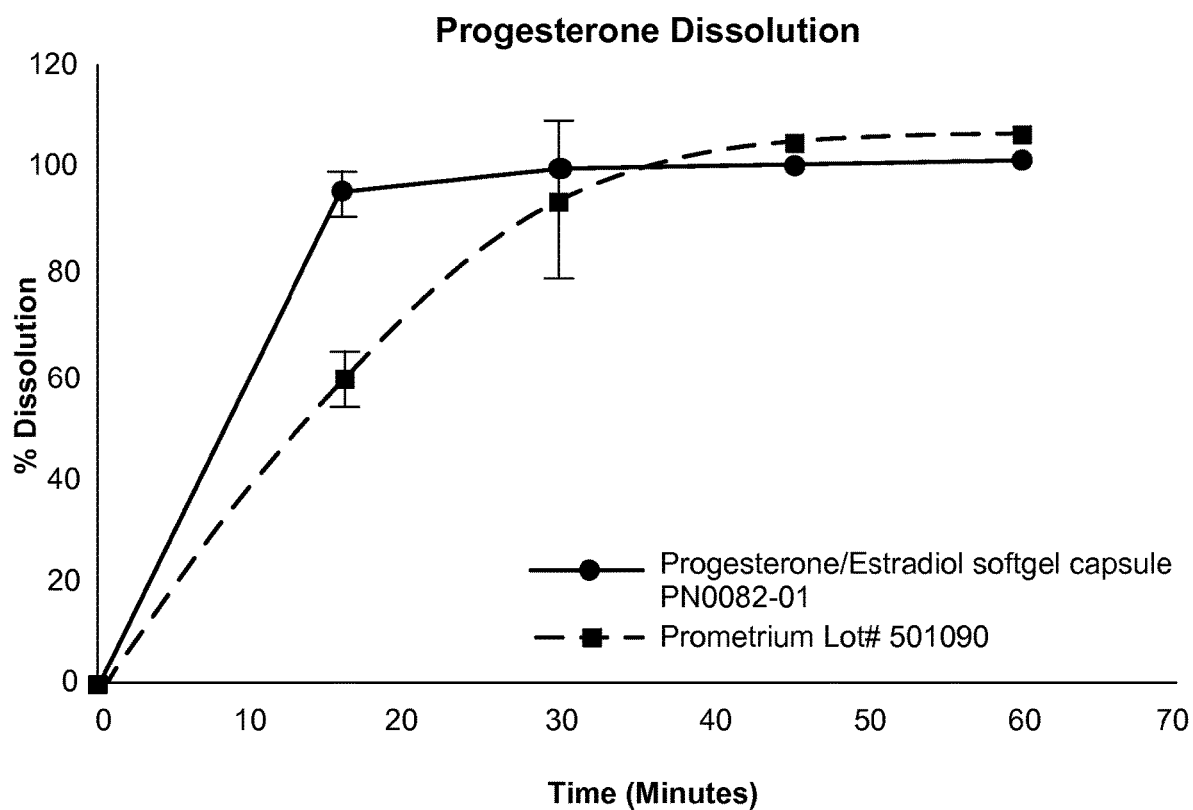


FIG. 6

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**PROGESTERONE FORMULATIONS****CROSS-REFERENCE TO RELATED APPLICATIONS**

This application is a National Stage application under 35 U.S.C. § 371 of International Application Serial No. PCT/US2013/046442, entitled "PROGESTERONE FORMULATIONS" which was filed on 18 Jun. 2013, and claims priority to the following U.S. patent applications: U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS," which was filed on Jun. 20, 2012; U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Nov. 21, 2012; U.S. Patent Application Serial No. PCT/US2013/023309, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Jan. 25, 2013; U.S. patent application Ser. No. 13/843,362, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Mar. 15, 2013; and U.S. patent application Ser. No. 13/843,428, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Mar. 15, 2013. All aforementioned applications are hereby incorporated by reference herein in their entirety.

**FIELD OF INVENTION**

The disclosure relates to progesterone formulations. Various progesterone formulations may be used in hormone therapies for menopausal, peri-menopausal and post-menopausal females, for example, to mitigate side effects from estrogen replacement therapy. In addition, various progesterone formulations may be used to prevent preterm delivery in pregnant women having a shortened cervix.

**BACKGROUND OF THE INVENTION**

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to supplement hormone levels in women who lack adequate hormone production. It can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones.

HRT is available in various forms. One therapy involves administration of low dosages of one or more estrogen(s) or one or more chemical analogues. Another involves administration of progesterone or one or more chemical analogues. Among other effects, progesterone administration acts to mitigate certain undesirable side effects from estradiol administration or naturally-occurring elevated blood levels including endometrial hyperplasia (thickening) and prevention or inhibition of endometrial cancer. Progesterone is a C-21 steroidal sex hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen. Like other steroids, progesterone consists of four interconnected cyclic hydrocarbons. Progesterone is hydrophobic, having a reported aqueous solubility of  $0.007 \pm 0.0$  mg/ml. Progesterone is poorly absorbed when administered orally.

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Conventional progesterone therapeutics include the administration of PROMETRIUM (progesterone, USP) (Abbott Laboratories, Chicago, Ill.). PROMETRIUM is an FDA-approved drug, formulated in a peanut oil-based medium, containing micronized progesterone, but with a relatively large particle size fraction.

The active ingredient is considered to be structurally identical to naturally occurring progesterone produced by a woman's body (also known as a "bioidentical").

Clinical trials involving PROMETRIUM have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean pharmacokinetic parameters listed in Table 1 (see Table 1, package insert for PROMETRIUM).

TABLE 1

Parameter	Pharmacokinetic Parameters of PROMETRIUM Capsules		
	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
$C_{max}$ (ng/ml)	$17.3 \pm 21.9$	$38.1 \pm 37.8$	$60.6 \pm 72.5$
$T_{max}$ (hr)	$1.5 \pm 0.8$	$2.3 \pm 1.4$	$1.7 \pm 0.6$
AUC (0-10)(ng × hr/ml)	$43.3 \pm 30.8$	$101.2 \pm 66.0$	$175.7 \pm 170.3$

The unusually high variability in the  $C_{max}$  and AUC, as evidenced by the large reported standard deviation, indicates that a significant percentage of patients are overdosed or receive a sub-optimal dose.

The presence of peanut oil in the formulation excludes patients who are allergic to peanut oil. Peanut oil, like other peanut products, may act as an allergen. Indeed, there is a portion of the population that has severe reactions to peanut oil. Peanut allergies are becoming a significant health concern. Food allergies are a leading cause of anaphylaxis, with approximately 200 deaths occurring annually in the United States. While incidence and prevalence are not entirely known, it is suspected that about 6% of children and 4% of adults in North America are affected by food allergies. Many food allergies experienced by children are generally outgrown in adulthood with the exception of peanut allergies.

Progesterone and its analogues can be used to treat a variety of medical conditions, including acute diseases or disorders, as well as chronic diseases and disorders associated with long-term declines of natural progesterone levels.

Accordingly, improved formulations of progesterone would be advantageous.

**SUMMARY OF THE INVENTION**

Various pharmaceutical formulations are disclosed herein. For example, pharmaceutical formulations are disclosed comprising ultra-micronized progesterone. Moreover, pharmaceutical formulations are disclosed comprising formulations of ultra-micronized progesterone, wherein the ultra-micronized progesterone is combined with a suitable excipient.

Thus, in various illustrative embodiments, the invention comprises an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical ingredient, in micronized form, in solubilized form, or in micronized and partially soluble form in a carrier that comprises a medium chain fatty



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acid-glycol ester or mixtures thereof and a non-ionic surfactant comprising a polyethylene glycol fatty acid ester. In some such embodiments the progesterone is ultra-micronized. In some such embodiments, at least about 80 wt % of the total progesterone is micronized. The fatty acids can be predominantly (>50 wt %): C6 to C12 fatty acids, C6 to C10 fatty acids, C8 to C12 fatty acids, or C8 to C10 fatty acids, the esters can be mono-, di-, or triesters or mixtures thereof, and the glycols can be glycerol, polyethylene glycol or propylene glycol or mixtures thereof. Some embodiments comprise a non-ionic surfactant that comprises C8 to C18 fatty acid esters of glycerol and polyethylene glycol.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings are included to provide a further understanding of the disclosure and are incorporated in and constitute a part of this specification, illustrate embodiments of the disclosure, and together with the description serve to explain the principles of the disclosure.

FIG. 1 illustrates a process to produce fill material in accordance with various embodiments;

FIG. 2 illustrates a process to produce softgel capsules in accordance with various embodiments;

FIG. 3 illustrates a process to produce softgel capsules in accordance with various embodiments; and

FIG. 4 illustrates a dissolution study of a formulation in accordance with various embodiments.

FIG. 5 illustrates a graph of the particle distribution obtained in Example 10.

FIG. 6 illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

#### DETAILED DESCRIPTION OF THE ILLUSTRATED EMBODIMENTS

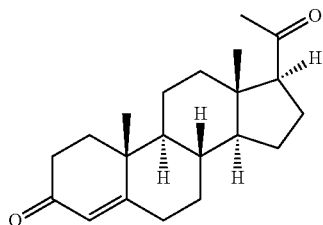
According to various embodiments, a pharmaceutical formulation comprising ultra-micronized progesterone is provided. As described in detail here, various carriers, lubricants, and other excipients may be included. In further embodiments, ultra-micronized progesterone formulations provide improved bioavailability and other pharmacokinetic improvements.

#### Definitions

Unless otherwise specified, the following definitions apply.

The term “ultra-micronized progesterone,” as used herein, includes micronized progesterone having an X50 value below about 20 microns and/or having an X90 value below about 25 microns.

A chemical structure of progesterone is depicted below:



The term “administer,” “administration,” “deliver” or “delivery” (collectively “administration”), as used herein,

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means administration to the body via, without limitation, tablets, capsules, softgel capsules, injections, transdermal patches, creams, gels, vaginal suppositories including gels or other mechanisms known in the art or hereinafter developed. The term “administration” may also mean direct application of softgel contents into the vagina, such as by accessing the softgel contents opening or rupturing the softgel capsule to liberate the contents therein.

The term “X50,” as used herein, means that half of the particles in a sample are smaller in diameter than a given number. For example, ultra-micronized progesterone having an X50 of 5 microns means that, for a given sample of ultra-micronized progesterone, half of the particles have a diameter of less than 5 microns. In that regard, similar terms, in the form XXX mean that YY percent of the particles in the sample are smaller in diameter than a given number. For example, X90 means that ninety percent of the particles in a sample are smaller in diameter than a given number.

The term “medium chain,” as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances. For further illustration, C6-C14 fatty acids, C6-C12 fatty acids, and C8-C10 fatty acids are all medium chain fatty acids and may be used in instances in which this specification calls for use of medium chain fatty acids, e.g., medium chain fatty acid esters of glycerol or other glycols.

The term “uniform distribution” means at least one of uniform dispersion, solubility, or lack of agglomeration of progesterone in gastric juices compared to PROMETRIUM.

The term “gastric juices” means the watery, acidic digestive fluid that is secreted by various glands in the mucous membrane of the stomach and consists chiefly of hydrochloric acid, pepsin, rennin, and mucin.

The term, “API,” as used herein, refers to active pharmaceutical ingredient. In formulations, the API is progesterone.

The term “excipients,” as used herein, refers to non-API substances such as carriers, solvents, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to humans according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term “carrier,” as used herein, means any substance or mixture of substances that may be mixed with or contain an API (e.g., ultra-micronized progesterone).

The term “capsule,” as used herein, refers to a generally safe, readily dissolvable enclosure for carrying certain pharmaceutical products, and includes hard or soft shell capsules.

The term “softgel,” includes soft shell capsules, including soft-gelatin capsules and soft vegetable-based capsules, and soft capsules made from other materials providing the composition of such soft capsules are compatible with the formulations of the various embodiments described herein. A softgel may comprise two primary phases: a gel or vegetable-based capsule and a fill material of the pharmaceutical formulation as described herein.

The term “bioavailability,” as used herein means the concentration of an active ingredient (e.g., progesterone) in the blood (serum or plasma). The relative bioavailability may be measured as the concentration in the blood (serum or plasma) versus time. Other pharmacokinetic (PK) indicators may be used to measure and assess bioavailability, determined by suitable metrics including AUC,  $C_{max}$  and optionally  $T_{max}$ .

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The terms “pharmacokinetics” and “pharmacokinetic measurements” include assessments and determinations to study absorption, distribution, metabolism, and excretion of a drug.

The term “AUC,” as used herein, refers to the area under the curve that represents changes in blood concentration of progesterone over time.

The term, “ $C_{max}$ ” as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of progesterone over time.

The term, “ $T_{max}$ ” as used herein, refers to the time that it takes for progesterone blood concentration to reach the maximum value.

Optionally, the term, “ $T_{1/2}$ ” as used herein, refers to the time that it takes for progesterone blood concentration to decline to one-half of the maximum level.

Collectively AUC,  $C_{max}$ , and optionally  $T_{max}$  and  $T_{1/2}$ , are the principle pharmacokinetic parameters that can characterize the pharmacokinetic responses of a particular drug product such as progesterone in an animal or human subject.

#### DESCRIPTION

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone, and fully solubilized progesterone, wherein said formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by Prometrium® when administered at equal dosage strengths.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %, based on the weight of the entire fill, i.e., the liquid pharmaceutical formulation.

Other embodiments disclosed herein further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, when compared to equal dosages of PROMETRIUM. Blood level variability is also compared at equal sampling times following administration.

According to the PROMETRIUM prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean PK parameters listed in the following table:

Parameter	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
$C_{max}$ (ng/ml)	17.3 +/- 21.9	38.1 +/- 37.8	60.6 +/- 72.5
$T_{max}$ (hr)	1.5 +/- 0.8	2.3 +/- 1.4	1.7 +/- 0.6
AUC <sub>0-10</sub> (ng × hr/ml)	43.4 +/- 30.8	101.2 +/- 66.0	175.7 +/- 170.3

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In particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM can be demonstrated via a fed bio-study such as that described below.

Other aspects of the present disclosure include the use of formulations as described herein wherein progesterone is at least one API in said formulation for the treatment of an animal, especially a mammal, including humans: for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone (collectively, “Progesterone-deficient States”) in a subject in need of treatment, and with a non-toxic effective amount of said formulations.

As used herein, the term “treatment”, or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, “prophylaxis” refers to administration of the active ingredient(s) to an animal especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200 mg, 250 mg, 300 mg, 350 mg and 400 mg.

Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the “Beckman Device”) may be used to determine particle size. Particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module (“ULM”). The ULM is capable of suspending samples in the size range of 0.017  $\mu$ m to 2000  $\mu$ m. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butanol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant (“Coulter 1B”), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The

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Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4  $\mu\text{m}$  to 2000  $\mu\text{m}$ . The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

In various embodiments, ultra-micronized progesterone has an X50 value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns; and an X90 value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

In various embodiments, ultra-micronized progesterone is formulated with peanut and peanut-oil free excipients.

In various embodiments, the carrier is selected to enhance dissolution and suspension properties of progesterone. In further various embodiments, the carrier is selected to enhance absorption of the API by cells of a mammal. For example, certain carriers may be selected to enhance absorption of the other formulation components, including the API. Absorption may comprise absorption into any cell and particularly absorption into digestive system cells, such as intestinal cells, and cells of the female reproductive system, such as the vagina and the cervix. Selected mono/di/triglycerides are particularly suited to aid in cellular absorption.

In various embodiments, the carrier may comprise medium chain fatty acids. Suitable carriers include caproic fatty acid; caprylic fatty acid; capric fatty acid; lauric acid; myristic acid; linoleic acid; succinic acid; glycerin; propylene glycol; caprylic/capric triglycerides; caproic/caprylic/capric/lauric triglycerides; caprylic/capric/linoleic triglycerides; caprylic/capric/succinic triglycerides; polyethylene glycol; propylene glycol dicaprylate/dicaprate; and combinations and derivatives thereof.

Suitable carriers further include esters of saturated coconut and palm kernel oil and derivatives thereof, including fractionated coconut oils and palm kernel oils thereof; and triglycerides of fractionated vegetable fatty acids, and derivatives thereof and combinations thereof. In further various embodiments, the carrier may comprise one or more monoglycerides, diglycerides, triglycerides, and combinations thereof. Such a suitable carrier is available commercially under the trademark MIGLYOL (caprylic/capric triglyceride) (Sasol Germany, GmbH). MIGLYOL products comprise esters of saturated coconut and palm kernel oil-derived caprylic and capric fatty acids, glycerin and/or propylene glycol. Suitable MIGLYOL products include MIGLYOL 810 (Caprylic/Capric Triglyceride) MIGLYOL 812 (Caprylic/Capric Triglyceride), MIGLYOL 818 (Caprylic/Capric/Linoleic Triglyceride) and MIGLYOL 829 (Caprylic/Capric/Succinic Triglyceride).

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Additional examples include a polyethylene glycol glyceride (Gelucire®; GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (Capmul® PG-8 and 10; the CAPMUL brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: Transcutol); diethylene glycol monoethyl ether; esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof. In other aspects and embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL (Diethylene glycol monoethyl ether) and MIGLYOL; TRANSCUTOL, MIGLYOL and CAPMUL PG-8 (Propylene Glycol Monocaprylate) and/or CAPMUL PG-10 (Propylene Glycol Monocaprate); CAPMUL MCM (Medium Chain Mono- and Diglycerides); CAPMUL MCM and a non-ionic surfactant; and CAPMUL MCM and GELUCIRE (a polyethylene glycol glyceride).

Various ratios of these oils can be used for suspension and/or solubilization of progesterone. CAPMUL MCM and a non-ionic surfactant, e.g., GELUCIRE 44/14 (Lauroyl macrogol-32 glycerides EP Lauroyl polyoxyl-32 glycerides NF Lauroyl polyoxylglycerides (USA FDA IIG)), can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, CAPMUL MCM and GELUCIRE were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. Thus, useful ratios can be, e.g., 8:1 or greater, e.g., 60 to 70:1.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In illustrative embodiments, oils used to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters, (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated. In illustrative embodiments, progesterone is soluble in the oils at room temperature, although it may be desirable to warm certain oils initially during manufacture to improve viscosity. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50° C., e.g., at or below 50° C., at or below 40° C., or at or below 50° C. In illustrative embodiments, GELUCIRE 44/14 is heated to about 65° C. and CAPMUL MCM is heated to about 40° C. to facilitate mixing of the oil and non-ionic surfactant, although such heating is not necessary to dissolve the estradiol or progesterone.

In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8



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wt % or higher, or 1.0 wt % or higher. Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, CAPMUL MCM, CAPMUL MCM C10 (Glyceryl Monocaprate), CAPMUL MCM C8 (Glyceryl Monocaprylate), and CAPMUL MCM C8 EP (Glyceryl Monocaprylate). These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, MIGLYOL 810 and MIGLYOL 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, CAPMUL PG-8, CAPMUL PG-2L EP/NF (Propylene Glycol Dilaurate), CAPMUL PG-8 NF (Propylene Glycol Monocaprylate), CAPMUL PG-12 EP/NF (Propylene Glycol Monolaurate) and CAPRYOL (Propylene glycol monocaprylate (type II) NF). Other illustrative examples include MIGLYOL 840 (Propylene Glycol Dicaprylate/Dicaprate).

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others, GELUCIRE 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol. Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of GELUCIRE, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids.

It will be understood that commercially available fatty acid esters of glycerol and other glycols are often prepared from natural oils and therefore may comprise components additional to the fatty acid esters that comprise the predominant (by weight) component(s) and that therefore are used to characterize the product. Such other components may be, e.g., other fatty acid triglycerides, mono- and diesters, free glycerol, or free fatty acids. So, for example, when an oil/solubilizing agent is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for CAPMUL MCM C8 describes CAPMUL MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as <=1% C6, >=95% C8, <=5% C10, and <=1.5% C12 and higher.

By way of further example, MIGLYOL 812 is generally described as a C8-C10 triglyceride because the fatty acid composition is at least about 80% caprylic (C8) acid and capric (C10) acid. However, it can also comprise small amounts of other fatty acids, e.g., less than about 5% of caproic (C6) acid, lauric (C12) acid, and myristic (C14) acid.

Specifically, a product information sheet for MIGLYOL by SASOL provides the composition of fatty acids as follows:

Tests	810	812	818	829	840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2
Myristic acid (C14:0)	max. 1.0	max. 1.0	max. 1	max. 1	max. 1

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-continued

Tests	810	812	818	829	840
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

Where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in C8-C10 triglycerides, and a thickening agent, it will be understood that the fatty acid esters component of the formulation may be, e.g., MIGLYOL 812 or a similar product.

By way of further illustration, GELUCIRE 44/14 is generally described as lauroyl polyoxyl-32 glycerides, i.e., polyoxyethylene 32 lauric glycerides (which is a mixture of mono-, di-, and triesters of glycerol and mono- and diesters of PEGs) because the fatty acid composition is 30 to 50% lauric acid and smaller amounts of other fatty acids, e.g., up to 15% caprylic acid, up to 12% capric acid, up to 25% myristic acid, up to 25% palmitic acid, and up to 35% stearic acid. The product may also contain small amounts of non-esterified glycols. Where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising C8 to C18 fatty acid esters of glycerol and polyethylene glycol, it will be understood that the thickening agent component of the formulation may be, e.g., GELUCIRE 44/14 or a similar product.

Similarly, where certain embodiment of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising PEG-6 stearate, ethylene glycol palmitostearate, and PEG-32 stearate, it will be understood that the thickening agent component of the formulation may be, e.g., TEFOSE 63 (PEG-6 stearate and ethylene glycol palmitostearate) or a similar product.

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., CAPMUL MCM) and polyethylene glycol glycerides (e.g., GELUCIRE) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65 C in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The progesterone can be added as the mixture cools, e.g., to below about 40 C or to below about 30 C, even down to room temperature.

In certain embodiments, an anionic and/or a non-ionic surfactant is used. Exemplary non-ionic surfactants may include one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as GELUCIRE, including, for example, GELUCIRE 44/11 and GELUCIRE 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, GELUCIRE 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, Tables below. Other non-ionic surfactants include, e.g., LABRASOL (Caprylocaproyl macrogol-8 glycerides EP Caprylocaproyl polyoxyl-8 glycerides NF PEG-8

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Caprylic/Capric Glycerides (USA FDA IIG)) (Gattefosse) and LABARAFIL (corn/apricot oil PEG-6 esters) (Gattefosse).

In various embodiments, a lubricant is used. Any suitable lubricant may be used, such as, for example and without limitation, lecithin, and in various embodiments, a mixture of polyethylene glycol ("PEG") esters, glycerides, and PEG, such as is commercially available under the trade name GELUCIRE (Gattefosse, FR) may also be used as a lubricant. Suitable lubricants may also comprise calcium stearate, ethyl oleate, ethyl laureate, glycerin, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium, oxide, magnesium stearate, poloxamer, glycols, and phospholipid mixtures. In particular, a mixture of polyethylene glycol esters, glycerides, and PEG such as GELUCIRE 44/14, may be used as a lubricant. GELUCIRE 44/14 is a non-ionic water dispersible surfactant, also known as lauroyl macrogol-32 glycerides EP and lauroyl polyoxyl-32 glycerides NF. In various embodiments, GELUCIRE 44/14 acts as a suspension agent.

In various embodiments, an antioxidant is used. Any suitable antioxidant may be used, such as, for example and without limitation, butylated hydroxytoluene. Butylated hydroxytoluene, a derivative of phenol, is lipophilic and is thus suited to being intermixed with ultra-micronized progesterone and carriers disclosed or contemplated herein.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

Thus, an illustrative embodiment of a pharmaceutical composition of the invention comprises progesterone, at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of one or more glycols, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized.

Pharmaceutical formulations in accordance with various embodiments comprise ultra-micronized progesterone. In further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, a carrier, and a lubricant. In still further embodiments a pharmaceutical formulation comprises ultra-micronized progesterone, a carrier, a lubricant, and optionally an antioxidant. In still further

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embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, and a medium chain triglyceride as a carrier. In still further embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone, and monoglycerides/diglycerides/triglycerides of caprylic/capric acid as a carrier. Various further embodiments also comprise lecithin and optionally butylated hydroxytoluene.

In additional embodiments, a pharmaceutical formulation comprises ultra-micronized progesterone and at least one carrier, a lubricant, optionally an antioxidant, and other pharmaceutically acceptable excipients. For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

Formulations in accordance with various embodiments may be administered alone or combination with one or more other drugs (or as any combination thereof). For example, formulations in accordance with various embodiments may also comprise estradiol.

In various embodiments, ultra-micronized progesterone is administered in a capsule. Capsules may be prepared using one or more film forming polymers. Suitable film forming polymers include natural polymers, such as gelatin, and synthetic film forming polymers, such as modified celluloses. Suitable modified celluloses include, but are not limited to, hydroxypropyl methyl cellulose, methyl cellulose.

Hard or soft shell capsules can be used to administer the API. In certain embodiments, capsules may be prepared by forming the two capsule halves, filling one of the halves with the fill solution, and then sealing the capsule halves together to form the finished capsule.

Hard shell capsules may be prepared by combining the "Body" and the "Cap". The "Body" of the capsule is filled with the "fill mass" and then closed with the "Cap". The "Body"/"Cap" interface is then sealed/banded.

Soft gelatin capsules may be prepared using a rotary die encapsulation process, as further described below.

Suitable shell additives, for either a hard or soft shell capsules, may include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids, and combinations thereof. The main ingredients of the capsule shell is primarily gelatin (or a gelatin substitute for non-gelatin capsules), plasticizer, and purified water. Hard shell and soft shell capsules differ primarily in the amount of plasticizer present that is used in the capsule shell.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include, but are not limited to, glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light-sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.



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Colorants can be used for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to minimize cross-linking of the gelatin.

In accordance with various embodiments, a softgel dosage form is used.

A softgel comprises two primary phases: a gel capsule and a fill material. The softgel may comprise a gelatin material in a relatively solid or stiff form. The softgel may define an inner volume that may contain the fill material. Dissolution of the softgel may commence at various points, such as along the digestive tract (mouth, esophagus, stomach and intestines), or other body cavities, such as the vaginal cavity.

As the softgel dissolves, the inner volume may come into fluid communication with the digestive system, allowing the fill material to leach outside the softgel. A softgel may also be punctured, cut, or otherwise opened outside a body. The fill material may then be poured or squeezed outside the gel capsule and applied on or in the body, such as within the vaginal cavity.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl esters (collectively known as "parabens") or combinations thereof.

The fill material may comprise a liquid, such as an oil, a solution, a suspension, or other acceptable forms. The active ingredient or active ingredient may be contained within the liquid.

Formulations in accordance with various embodiments may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Ultra-micronized progesterone in accordance with various embodiments may be formulated as a vaginal suppository or vaginal cream for administration onto the vulva or into the vagina, cervix, or uterus of a human. Capsules (e.g., softgels) containing ultra-micronized progesterone also may be administered vaginally, including insertion of a capsule directly into the vaginal cavity or delivery of such capsule contents into the vaginal cavity. Ultra-micronized progesterone, in accordance with various embodiments, may be formulated for intraperitoneal administration, and atomization, such as with nasal mist administration.

In accordance with various embodiments, enhanced bioavailability of progesterone is provided, such as over conventional progesterone formulations wherein it is well known that commercially available formulations of progesterone are poorly or inconsistently absorbed. While not bound by theory, the elements of the present formulation provide the enhanced performance characteristics as further described herein, including, for example and without limitation, improved bioavailability and the potential to be able to reduce the administered dosage strength compared to

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presently available progesterone formulations. Bioavailability comparisons to commercially available forms, such as tablet forms, may be determined by standard pharmacokinetic techniques

In accordance with various embodiments, food effects are reduced, e.g., relative to comparative progesterone products.

In accordance with various embodiments, formulations do not include peanut oil. The lack of peanut oil obviates the risk posed to those having peanut-based allergies.

Capsules may be arranged in blisters or cartridges or bottles.

According to various embodiments, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having delivery days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no API or hormone (e.g., progesterone) may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each dose (e.g., each softgel) may contain ultra-micronized progesterone in amounts of 100 mg, 150 mg, 200 mg, and 250 mg, though other dose ranges are contemplated herein. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

Formulations in accordance with various embodiments may be used to treat or prevent preterm delivery in pregnant women, including in certain women having a shortened cervix. In various embodiments, a capsule, for example a softgel capsule, may be opened and the fill material applied in or around the vagina. However, in various embodiments the capsules are taken orally.

Formulations in accordance with various embodiments may be used to treat or prevent endometrial hyperplasia.

Formulations in accordance with various embodiments may be used to treat or prevent secondary amenorrhea.

Formulations in accordance with various embodiments may be used to mitigate or treat the effects of estradiol supplementation. In particular, formulations in accordance with various embodiments may be co-administered with estradiol and/or co-formulated with estradiol.

Formulations in accordance with various embodiments may be used to treat menopause-related symptoms, including vasomotor symptoms, for example, in relation to treatment of hypoestrogenism related symptoms including hot flashes and night sweats (vasomotor symptoms), sleep disturbances, mood changes, vulvo-vaginal atrophy; and osteoporosis and endometrial hyperplasia reduction.

Additional objects of the present disclosure include: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

#### Specific Embodiments

Through extensive trial-and-error testing of various fatty acid esters of glycerol and other glycols, embodiments of the

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invention have been invented that have one or more favorable characteristics for development as a human drug product. Such favorable characteristics include those described above, e.g., improved PK and reduced variability.

Such embodiments include an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical ingredient, in micronized form suspended in a carrier that comprises a medium chain fatty acid-glycol ester or mixtures thereof and a non-ionic surfactant comprising a polyethylene glycol fatty acid ester.

A more specific such embodiment is such formulation wherein the progesterone is ultramicrosized.

In certain such embodiments, the progesterone is suspended and/or solubilized in one or more C6 to C12 fatty acid mono-, di-, or triesters of glycerol, e.g., one or more C6 to C14 triglycerides, e.g., one or more C6 to C12 triglycerides, such as one or more C8-C10 triglycerides. An example of a carrier that provides beneficial properties is C8, C10, or C8 and C10 saturated triglycerides, such as but not limited to MIGLYOL, e.g., MIGLYOL 812.

In such general and more specific embodiments, the non-ionic surfactant is a polyethylene glycol saturated or unsaturated fatty acid ester or diester. In certain such embodiments, the non-ionic surfactant comprises C8 to C18 fatty acid esters of glycerol and polyethylene glycol. An example of a non-ionic surfactant that provides beneficial properties is GELUCIRE, e.g., GELUCIRE 44/14.

In certain such embodiments, the non-ionic surfactant has a HLB value of about 15. An illustrative example of such surfactant is GELUCIRE 44/14.

As noted above, such formulations are liquid at room temperature, not gels, hard fats, or any other solid form. The non-ionic surfactant serves to increase viscosity. In some such embodiments, the non-ionic surfactant, e.g., GELUCIRE or TEFOSE, may be solid at room temperature and require melting to effect mixing with the estradiol solubilized in fatty acid-glycol esters but the resultant formulation is advantageously liquid, not solid.

The formulation of such embodiments is typically encapsulated in a soft gelatin capsule or other soft capsule.

Typically, such formulations do not comprise a bioadhesive (i.e., muco-adhesive) agent, a gelling agent, or a dispersing agent, or, at least, do not comprise one or two of such components.

In more specific such formulations, the capsule shell, the active pharmaceutical ingredient, the fatty acid esters and the non-ionic surfactant are the only essential ingredients. Non-essential ingredients, e.g., colorants, antioxidants or other preservatives, etc., may, of course, be included but other ingredients in amounts that would materially change the solubility of the progesterone, the PK of the encapsulated formulation, or other clinically relevant properties, e.g., other oils or fatty acid esters, lecithin, muco-adherent agents, gelling agents, dispersing agents, or the like would not be included. Such embodiments of the invention may be described as consisting essentially of the capsule shell, the active pharmaceutical ingredient, the fatty acid esters and the non-ionic surfactant, as described in the immediately preceding paragraphs describing illustrative embodiments discovered to have favorable characteristics.

As an example of such embodiments discovered to have such favorable characteristics is mentioned the product identified in Example 2, Table 3, below.

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## EXAMPLES

## Example 1

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 2

Ingredient	mg/Capsule	%	Function
Ultra-micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 2

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 3

Ingredient	%	mg/Capsule	Function
1. Ultra-micronized Progesterone	30.77	200.00	Active
2. Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
3. Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	3.00	19.50	Suspending Agent
4. Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 3

## Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL, including without limitation MIGLYOL 812, may be used in embodiments comprising a suspension of progesterone.

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As can be seen in Table 9, the solubility of progesterone in CAPMUL MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg.

TABLE 4

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM	73.4
CAPMUL PG8	95
MIGLYOL 812	27.8
CAPMUL MCM: GELUCIRE 44/14 (9:1)	86.4
CAPMUL MCM: GELUCIRE 44/14 (7:3)	70.5
CAPMUL MCM: GELUCIRE 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL MCM in combination with GELUCIRE 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL MCM and GELUCIRE 44/14 system, wherein the ratio of CAPMUL MCM to GELUCIRE 44/14 is 9:1.

TABLE 5

Ingredient	Progesterone Solubility (mg/g)
CAPMUL MCM:GELUCIRE 44/14 (9:1)	86.4
CAPMUL MCM:GELUCIRE 44/14 (7:3)	70.5
CAPMUL MCM:GELUCIRE 44/14 (6:4)	57.4

## Example 4

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 6

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL is heated to about 45° C. GELUCIRE 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

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In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 7

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/diglycerides/triglycerides of caprylic/capric acid (CAPMUL MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	6.0	1	Lubricant/Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL MCM is heated to about 65° C. GELUCIRE 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

## Example 5

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 8

Ingredient	%	mg/Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL 812 or equivalent)	65.93	428.55	Carrier
Lauroyl polyoxyl-32-glycerides (GELUCIRE 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL may be present in a range from about 35-95% by weight; GELUCIRE 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

## Example 6

## Bioavailability Assessment—Fasted

A randomized single-dose oral bioequivalence study comparing 200 mg ultra-micronized progesterone capsule test product (T) and 200 mg PROMETRIUM® (progesterone) capsules (Abbott Laboratories, Abbott Park, Ill.) reference product (R) is conducted. Subjects are administered a single 200 mg dose of either test product (T) or the reference product (R) under fasting conditions, for example, subjects fasted at least 10.0 hours prior to dosing. Blood is collected pre-dose and post-dose. Pre-dose samples are collected at approximately -01.00, -00.50, and 00.00 hours. Post-dose samples are collected at approximately 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 09.00, 10.00, 12.00,

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18.00, 24.00, 36.00 and 48.00 hours. Standard meals are provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00 and 37.00 hours post-dose.

Pharmacokinetic measurements are assessed including  $C_{max}$ , AUC and optionally  $T_{max}$ . Comparative bioavailability of the test product (T) and reference product are assessed.

## Example 7

## Bioavailability Assessment—Fed

The procedures for determining bioavailability under fasted conditions are repeated except that subjects are administered a single 200 mg dose of either test product (T) or reference product (R) immediately following a high fat meal, for example, within 30 minutes of dosing. Blood is collected pre-dose and post-dose. Pre-dose samples are collected at approximately -01.00, -00.50, and 00.00 hours. Post-dose samples are collected at approximately 01.00, 02.00, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 09.00, 10.00, 12.00, 18.00, 24.00, 36.00 and 48.00 hours. Standard meals are provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00 and 37.00 hours post-dose. Pharmacokinetic measurements are assessed including  $C_{max}$ , AUC and optionally  $T_{max}$ . Bioavailability of the test product (T) in reference to the reference product is assessed. The effect of food on the comparative bioavailability of the test product (T) and the reference product (R) are also assessed.

## Example 8

Method of manufacture in accordance with various embodiments are shown in FIGS. 1-3. With reference to FIG. 1, method of fill material, i.e. fill mass, preparation 100 is shown. Step 102 comprises mixing a carrier, a lubricant, and an antioxidant as described herein. For example, lecithin and butylated hydroxytoluene may be mixed with one or more medium chain mono-, di- or triglycerides, or combinations thereof. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 102 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $N_2$ . Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step 104 may comprise mixing ultra-micronized progesterone into the mixture of the carrier, the lubricant, and the antioxidant. A pasty substance is thus formed. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 104 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $N_2$ . Step 106 comprises degassing. The resulting mixture from step 106 may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. 2, softgel capsule, i.e. gel mass, production 200 is shown. Step 202 comprises mixing glycerin with water. The water used in step 202 may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 202 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $N_2$ . Heating may be performed until the temperature reaches  $80 \pm 5^\circ \text{C}$ .

Step 204 comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step 204 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $N_2$ . A vacuum may be drawn in step 204 to de-aerate.

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Step 206 comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step 206 may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas  $N_2$ . Step 208 comprises degassing. The resulting mixture from step 208 may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. 3, softgel capsule assembly process 300 is shown. Step 302 comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to  $30^\circ \text{C.} \pm 3^\circ \text{C}$ . Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step 304 comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step 208 of FIG. 2. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of  $55^\circ \text{C.} \pm 10^\circ \text{C}$ . The wedge temperature may be  $38^\circ \text{C.} \pm 3^\circ \text{C}$ . The drum cooling temperature may be  $4^\circ \text{C.} \pm 2^\circ \text{C}$ . The encapsulator may be lubricated using MIGLYOL 812. Step 304 thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness  $0.85 \pm 0.05 \text{ mm}$  using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight  $\pm 5\%$  (i.e.,  $650 \pm 33 \text{ mg}$  and  $325 \pm 16.3 \text{ mg}$ ).

Step 306 comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Polishing may be performed with isopropyl alcohol.

## Example 9

## Stability Study

In accordance with various embodiments, formulations in accordance with various embodiments have an exemplary shelf life of 3 months with storage at  $25 \pm 2^\circ \text{C.} / 60 \pm 5\% \text{ RH}$  in 75 cc HDPE white, opaque bottles with a 38/400 mm white child resistant cap.

Packaging during testing comprises a 75 cc round HDPE bottle and 33 mm cap. A Brasken FPT 300F resin is associated with the cap. Testing criteria include visual appearance, assay of progesterone, dissolution, content uniformity and microbial limits testing.

Three test groups are created. Test group 1 comprises a test at  $40^\circ \text{C.} / 75\% \text{ RH}$ . Test group 2 comprises a test at  $30^\circ \text{C.} / 65\% \text{ RH}$ . Test group 3 comprises a test at  $25^\circ \text{C.} / 60\% \text{ RH}$ . Test group 1 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 1, 2, 3, and 6. Test group 2 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 0, 1, 2, 3, 6, and 12. Test group 3 is tested for visual appearance, assay of ultra-micronized progesterone, and dissolution at months 0, 1, 2, 3, 6, 12 and 24.

## Example 10

A particle size analysis is conducted by using a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device"). The Beckman Device uses laser



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diffraction to determine particle size. A sample of a formulation in accordance with various embodiments is provided. The Beckman Device particle sensor yields that the sample has an X50 of 6.67  $\mu\text{m}$ , an X75 of 14.78  $\mu\text{m}$ , and an X25 of 2.193  $\mu\text{m}$ .

## Example 11

A dissolution study was performed using a formulation in accordance with various embodiments. The results of the dissolution study are shown in FIG. 4.

The dissolution study was performed using a United States Pharmacopoeia dissolution apparatus 3 (reciprocating cylinder) ("USP Apparatus 3"). The USP Apparatus 3 was set to 30 dips per minute. Two hundred fifty mL (250 mL) of a solution of 1N HCL with 3% sodium lauryl sulfate was used at 37° C.

FIG. 4 shows dissolution percentage in the y axis over time in minutes on the x axis. A formulation in accordance with various embodiments is shown having circular dots, and is labeled formulation 402. An existing commercial pharmaceutical product containing progesterone is shown having square dots and is labeled existing product 404. As shown in FIG. 4, formulation 402 reaches a higher level of dissolution in a shorter time than existing product 404.

## Example 12

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279  $\mu\text{m}$ , an X75 of 7.442  $\mu\text{m}$ , and an X25 of 1.590  $\mu\text{m}$ . The Beckman Device also yielded that the mean particle size is 4.975  $\mu\text{m}$ , the median particle size is 4.279  $\mu\text{m}$ , the mode particle size is 6.453  $\mu\text{m}$ , and the standard deviation is 3.956  $\mu\text{m}$ . A graph of the particle distribution obtained is shown in FIG. 5.

## Example 13

Study 352—Progesterone and Estradiol Combination Study under Fed Conditions. This following study protocol was used to establish bio-availability and bioequivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula:

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Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	7.14	50.00
Estradiol Hemihydrate, USP Micronized	0.30	2.07
CAPMUL MCM, NF, USP	83.27	582.93
GELUCIRE 44/14, NF	9.29	650
Total	100.00	700

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study.

The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting.

Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively.

Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum.

Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and/or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.



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In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at -01.00, -00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of  $-70^{\circ}\text{C} \pm 20^{\circ}\text{C}$  in the bio-analytical facility until analysis.

Progesterone (Corrected and Uncorrected) and Estradiol (unconjugated) and estrone (total) in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters  $C_{max}$ ,  $AUC_{0-t}$  &  $AUC_{0-\infty}$  were calculated on data obtained from 24 subjects for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 9, below, for progesterone.

TABLE 9

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)				
Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean $\pm$ Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
$C_{max}$	47.0	43.0	$81.0 \pm 82.8$	$117.7 \pm 173.7$
$AUC_{0-t}$	107.6	97.8	$163.9 \pm 136.5$	$191.1 \pm 241.7$
$AUC_{0-\infty}$	110.7	110.0	$173.5 \pm 143.0$	$207.1 \pm 250.3$

\*Estimate of Least Square Mean used to calculate Geometric Mean

Study 351—Progesterone and Estradiol Combination Study Under Fasting Conditions.

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters  $C_{max}$ ,  $AUC_{0-t}$  &  $AUC_{0-\infty}$  were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 10, below for progesterone.

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TABLE 10

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)				
Pharmacokinetic Parameter	Geometric Mean*		Arithmetic Mean $\pm$ Standard Deviation	
	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product (R)
$C_{max}$	2.3	3.0	$2.9 \pm 2.3$	$3.9 \pm 3.4$
$AUC_{0-t}$	8.4	10.9	$11.2 \pm 8.7$	$14.5 \pm 11.0$
$AUC_{0-\infty}$	12.9	17.2	$15.1 \pm 9.0$	$19.6 \pm 10.2$

\*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to PROMETRIUM.

## Example 14

## Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of PROMETRIUM and comparing the dissolution of estradiol to the dissolution of Estrace. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37 C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from PROMETRIUM. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from Estrace. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from PROMETRIUM is attached as FIG. 6.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. The disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad, general meaning of the terms in which the

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appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

What is claimed:

1. A pharmaceutical composition comprising:  
progesterone and an effective amount of estradiol not exceeding 2 mg, wherein the estradiol and progesterone are present in a weight ratio of 1:100;  
a medium chain oil; and  
a non-ionic surfactant;  
further wherein the progesterone is present from about 20 to about 50 weight percent of the composition.
2. The pharmaceutical composition of claim 1, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.
3. The pharmaceutical composition of claim 1, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.
4. The pharmaceutical composition of claim 1, wherein the composition is provided in a gelatin capsule.
5. The pharmaceutical composition of claim 1, wherein the composition provides increased progesterone bioavailability compared to a micronized progesterone suspended in peanut oil.
6. The pharmaceutical composition of claim 1, wherein the medium chain oil comprises at least one C6-C14 fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.
7. The pharmaceutical composition of claim 6, wherein the at least one C6-C14 fatty acid mono-, di-, or tri-ester of glycerol is a C8 fatty acid mono-, di-, or tri-ester of glycerol.
8. The pharmaceutical composition of claim 6, further comprising a second C6-C14 fatty acid mono-, di-, or tri-ester of glycerol.
9. The pharmaceutical composition of claim 8, wherein the second C6-C14 fatty acid mono-, di-, or tri-ester of glycerol is a C10 fatty acid mono-, di-, or tri-ester of glycerol.
10. The pharmaceutical composition of claim 9, wherein the medium chain oil is CAPMUL MCM.

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11. The pharmaceutical composition of claim 1, comprising 50 mg of progesterone.

12. The pharmaceutical composition of claim 1, comprising 100 mg of progesterone.

13. The pharmaceutical composition of claim 12, wherein the progesterone is ultra-micronized and has an X50 less than or equal to 15 microns.

14. The pharmaceutical composition of claim 13, wherein the ultra-micronized progesterone has an X90 of less than about 25 microns.

15. The pharmaceutical composition of claim 12, wherein a portion of the progesterone is solubilized and a portion of the progesterone is suspended.

16. The pharmaceutical composition of claim 15, wherein the non-ionic surfactant is selected from the group consisting of lauroyl macrogol-32 glycerides EP, lauroyl polyoxyl-32 glycerides, and caprylocaproyl macrogol-8 glycerides EP.

17. The pharmaceutical composition of claim 16, wherein the composition is provided in a gelatin capsule.

18. The pharmaceutical composition of claim 16, wherein the composition provides increased progesterone bioavailability compared to a micronized progesterone suspended in peanut oil.

19. The pharmaceutical composition of claim 18, wherein the medium chain oil comprises at least one C6-C14 fatty acid mono-, di-, or tri-ester of glycerol or mono- or di-ester of a glycol.

20. The pharmaceutical composition of claim 19, wherein the at least one C6-C14 fatty acid mono-, di-, or tri-ester of glycerol is a C8 fatty acid mono-, di-, or tri-ester of glycerol.

21. The pharmaceutical composition of claim 20, further comprising a second C6-C14 fatty acid mono-, di-, or tri-ester of glycerol.

22. The pharmaceutical composition of claim 21, wherein the second C6-C14 fatty acid mono-, di-, or tri-ester of glycerol is a C10 fatty acid mono-, di-, or tri-ester of glycerol.

23. The pharmaceutical composition of claim 22, wherein the medium chain oil is CAPMUL MCM.

\* \* \* \* \*